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ALBAN KÖHLER

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In Memoriam

Einer der Pioniere der medizinischen Röntgenologie, Professor Dr. med. ALBAN KÖHLER, Ehrenmitglied des »Nordischen Vereins für Medizinische Radiologie», starb durch Herzschlag am 26. Februar d. J. in Neder-Selters i. Taunus und wurde den 3. März in Wiesbaden beerdigt.

ALBAN KÖHLER hatte seine originale Lebensart gefunden. Sein ganze Röntgenwirksamkeit, Praxis wie Schriftstellertum, hat er in seinem Hause, Theelemannstrasse 1 in Wiesbaden, allein vollbracht. Seine einzige Hilfe war bis zu ihrem Tode 1942 seine intelligente und aufopfernde Frau. Schon vorher scheint er indessen alle Röntgenarbeit selbst gemacht zu haben. So schreibt er mir d. 26. Nov. 1939: »Ich erledige meine Praxis ohne jede Hilfe weiter. Die Entwicklung der Filme ist mein Steckenpferd.»

Mit dem Eifer und der Hingebung eines Ansiedlers hat er das Leben hindurch mit einfachem Gerät, das er meisterhaft handhabte, die Grenzen der Röntgendiagnostik erweitert und mit scharfem und unbefangenem Auge die Ernte des Neulandes geprüft.

Unter den Pflanzen der Röntgenflora, welche seinen Namen zur Nachwelt gebracht haben, seien hier erwähnt: die »Köhlerschen Krankheiten» des Naviculare der Fusswurzel und des Metatarsale II, die Entdeckung, dass die Konturen der Niere sich gegen den Fettkapsel abzeichnen können und dass perinephritische Abscesse die Konturen der Niere und des M. psoas verwischen können, wie die epochemachende Einführung der Distanzaufnahme des Herzens anstatt der unsicheren »Orthodiagraphie». Als einer der ersten hat er weiter Serien-Röntgenaufnahmen zu primitiver Kinematographie zusammengestellt und die Stereoskopie innerer Organe wie auch das Photographieren von Schirmbildern vorgeschlagen.

ALBAN KÖHLERS Hauptwerk, das seinen Namen früh weltbekannt machte und dessen Vollführung sein ganzes Leben aufnahm, ist sein Lehrbuch, »Grenzen des Normalen und Anfänge des Pathologischen im Röntgenbild» genannt.

Die Bedeutung dieses Werkes muss in Zusammenhang mit der Rolle Deutschlands als Bahnbrecher für den Röntgenunterricht im Anfange des Jahrhunderts betrachtet werden. ALBERS-SCHÖNBERG und H. RIEDER haben ausgezeichnete Lehrbücher der Röntgendiagnostik geschaffen. R. GRASHEY und FRANZ M. GROEDEL brachten in ihren »Atlanten» ein kritisch beurteiltes Unterrichtsmaterial von typischen normalen und pathologischen Röntgenbildern, und in der Serie von Sonderbänden der »Fortschritte auf dem Gebiet der Röntgenstrahlen» wurden die Röntgenbefunde der medizinischen Spezialgebiete beleuchtet.

Ein besonderes Problem begegnete indessen der jungen Röntgen-

diagnostik, wenn es galt die Röntgenbilder mit den bekannten anatomischen Bildern zu vergleichen und in anatomische Begriffe zu übersetzen.

Normale Varianten und bedeutungslose Anomalien wie auch Veränderungen der Organkonturen durch ungewöhnliche Projektionen wurden leicht als pathologisch gedeutet, und die normalen funktionellen Variationen der Form, Lage und Grösse der Eingeweide waren sehr ungenügend bekannt. Wer die ersten Kinderjahre der Röntgendiagnostik erlebt hat weiss, wie auf diese Weise Irrtümer und Fehldeutungen bei jedem Schritt lauerten. Da kam 1910 KÖHLERS kleines »Lexikon der Grenzen des Normalen und der Anfänge des Pathologischen im Röntgenbilde», eine wahre Rettungsbrücke für die Röntgenanfänger.

Seitdem hat ALBAN KÖHLER durch riesige Arbeit mit der gewaltigen Entwicklung der Röntgenanatomie in neuen Auflagen seiner »Grenzen» gleichen Schritt zu halten versucht. Das Buch war von Anfang an als »Nachschlagewerk», als »Lexikon», gedacht und in einfacher, populärer Form dargestellt, »für Ärzte die in der Röntgenologie Anfänger sind und über noch keine reichliche Erfahrung verfügen». Diese Art und diese Fassung, welche gewiss dazu beigetragen haben, dem Werk seinen Weg durch die Welt zu bahnen, hat es behalten. Gegenstand und Umfang des Buches haben sich aber gemäss dem Gang der Entwicklung geändert. In der ersten Zeit war sein Hauptgegenstand so zu sagen, »die Grenzen des Normalen» oder mit anderen Worten normale Erscheinungen, welche pathologische Veränderungen vortäuschen können.

Mehr und mehr sind aber die »Anfänge des Pathologischen» Objekt der Darstellung geworden. Zwar hat nämlich die fortschreitende Entwicklung der technischen Hilfsmittel, welche unaufhörlich neue Gebiete der Diagnostik öffnen und immer feinere Einzelheiten hervortreten lassen, auch neue und unerwartete Fehlerquellen mit sich gebracht und zur Entdeckung neuer normaler Varianten geführt. Anderseits hat sich aber die ganze Röntgendiagnostik durch die Entwicklung der Technik und der Kenntnisse mehr und mehr auf die Diagnose gerade der Anfänge des Pathologischen, d. h. der frühen Veränderungen, gerichtet.

Die Arbeit ist in 8 deutschen Auflagen erschienen, die letzte im Jahre 1943, und in mehrere Sprachen übersetzt worden. Von 177 Seiten mit 73 Abbildungen ist sie auf 820 Seiten mit 565 Bildern angewachsen. Die Strichzeichnungen, welche bis zur fünften Auflage ausschliesslich

gebraucht wurden und nach wie vor überwiegen, sind sehr lehrreich. Di Autotypien von Röntgenbildern, welche danach hinzugefügt wurden sind teilweise von hauptsächlich historischem Interesse, ALBAN KÖHLER eigene altertümliche Bilder wiedergebend. Diese wurden auch von ihm selbst nur als »Notbehelfe» für den Text betrachtet.

KÖHLER hat die Ausgabe der »Grenzen» durchgeführt, teils auf Grund eigener Beobachtungen, hauptsächlich aber durch Literaturstudien und eine umfassende Korrespondenz. Besonders wertvoll ist der Umstand, dass die spärlichen Literaturangaben der ersten Auflage zu einem handlichen Anzeiger des aktuellen Schrifttums herangewachsen sind.

So haben sich KÖHLERS »Grenzen» zu einem umfassenden Nachschlagewerk über die feinere Röntgendiagnostik entwickelt.

Für die Röntgennovizen aller Welt — und sie werden immer die Mehrzahl der Röntgenleute ausmachen — ist der einsame Arbeiter ALBAN KÖHLER durch seine »Grenzen» ein ausserordentlicher Lehrer geworden, aber auch für Röntgenveterane ein hochgeschätzter Lotse in schweren Fahrwässern.

Wir hoffen, dass geschickte und pietätsvolle Hände sein Lebenswerk für kommende Geschlechter fruchtbar machen werden.

ALBAN KÖHLER war auf der Höhe seines Lebens ein ungewöhnlich glücklicher Mensch. Er freute sich kindlich über seine Erfolge und die Ehrenbezeugungen, die ihm reichlich zuteil wurden. In den Zeilen, mit welchen er für die Freundlichkeiten auf seinem 70-jährigen Geburtstage, den 1. März 1944, dankt, gibt er einen bezeichnenden Ausdruck für seine Persönlichkeit: »Von den 70 stand ich 45 Jahre meines an Glück und Freude reichen Lebens im Bereich und Banne der Wunderstrahlen Röntgens. Helfend und forschend möchte ich noch weiter darin verharren, solange es mir das Schicksal vergönnen mag.»

Schwer wurden aber seine letzten Jahre durch die Katastrophe Deutschlands verfinstert.

In Dezember 1942 wurden bei dem Fliegerangriff auf Leipzig rund tausend Stück der 8. Auflage der »Grenzen» vernichtet. Die 9. Auflage, die sofort in Angriff genommen wurde, war schon 1945 zu $^1/_4$ im Erstdruck fertig, als bei einem Fliegerangriff auf München alle Clichées vernichtet wurden, und dann kam der Zusammenbruch und seitdem musste alles unterbrochen werden. Bei der grossen Zerstörung Wiesbadens d.

2. 2. 1945 sind seine Wohnung, Institut sowie aller Besitz mit Ausnahme von 3 Handkoffern ein Raub der Flammen geworden.

Dann kam zu allem Jammer die Nachricht, dass sein einziges Kind, sein geliebter Sohn, der junge Kinderarzt BERNDT KÖHLER, Mitte März 1945, nach 5 Jahren Kriegesdienst an der Ostfront gefallen war. Er hinterliess einen Sohn, CHRISTOPH-ALBAN, $3^3/_4$ Jahre alt, und ein Töchterlein, VERONIKA, nach seinem Tod geboren.

Nach der Zerstörung Wiesbadens wohnte der alte KÖHLER unter kummervollen Umständen zusammen mit der Schwiegertochter und den Enkeln im Nieder-Selters i. Taunus nördlich von Wiesbaden. Trotz Alter und allem Unglück hat er, nicht Mut und Arbeitsvermögen verloren. Im Juni 1946 erzählt er, dass er »inzwischen» seine Memoiren: »Röntgenarztes Erdewallen, 750 Schreibeseiten», fertig gebracht hatte.

Die Schilderung seines langen und glücklichen Lebens hat dem alten Röntgenologen Trost geschenkt, und diese Arbeit gab ihm die Zuversicht wieder. In seinem letzten Briefe an mich, vom 13. 1. 47, gedenkt er im Frühjahr in Wiesbaden, im 74. Lebensjahre, wieder mit Praxis zu beginnen ...

Lange brauchte er doch nicht für die Existenz Kummer zu hegen. Barmherzig hat der Tod ihn über die Grenzen des Irdischen geführt.

GÖSTA FORSSELL.

FROM THE ROENTGEN THERAPY DEPARTMENT OF SÖDERSJUKHUSET, STOCKHOLM
(CHIEF: HUGO AHLBOM, M. D.)

RADIATION THROMBOCYTOPENIA[1]

(Preliminary report)

by

Harry Mossberg

Recently I have published in this journal an article called »Two cases of allergy-like reaction with hemorrhagic diathesis following roentgen treatment» (Zwei Fälle von allergie-ähnlicher Reaktion mit hämorrhagischer Diathese im Anschluss an Röntgenbehandlung). One of the patients, a man 62 years old, suffering from myastenia gravis, received roentgen treatment against thymus, *i. e.* to the upper part of the mediastinum, including sternum, the seize of the field about 100 cm². We gave 3,200 r during 8 days with a daily dosage of 400 r. (Skin-target distance 40 cm, 170 kv, 15 ma, ½ mm Cu + 1 mm Al). On the very same day, that the treatment was finished, the patient was taken ill with symptoms of hemorrhagic diathesis. He showed widespread small hemorrhages in the cutis and bloodstained expectorations. The skin reaction on the field of treatment was very intense. A thrombocytopenia with a lowest count of 23,000 thrombocytes was recorded. After a week the patient improved but about one month after the roentgen treatment he got a recurrence of his hemorrhagic diathesis. Even at this time he suffered from a productive hemorrhagic cough. This time the bleedings in the skin did not disappear until after one month. He entered the hospital a week after the beginning of the recurrence and the thrombocytic count was then 69,000, the following day 87,000. Hereafter the thrombocytic count varied between 90,000 and 180,000. In the beginning the bleeding time was increased to thirty minutes and it was gradually normalized during two and a half months. No other disturbances of the coagulation could be discovered. The patient died in his hemorrhagic diathesis about four months after the roentgen treatment had been finished.

The other case presented a more violent course. The patient, a woman 75 years old, was given 3 or 4 times 600 r on each of six thoracic fields

[1] Submitted for publication, Oct. 12. 1946.

or a cancer of the oesophagus (totally 11,400 r during 26 days). The eize of each field was 100 cm². (Skin-target distance 60 cm, 170 kv, 15 ma, ½ mm Cu + 1 mm Al). At this time an acute hemorrhagic diathesis appeared preceeded by a very intense urticaria and as in the previous case it was combined with a very pronounced epidermitis with exudative reaction on the fields of treatment. No other disturbances of the clotting mechanism than a thrombocytopenia with a lowest count of 98,000 thrombocytes could be found. Except the bleedings in the skin which like the urticaria were most marked around the fields of treatment, as if originating from them, the hemorrhagic diathesis gave rise to a productive hemorrhagic cough and a slight bleeding from the vagina. The patient died a fortnight after the onset of the diathesis. The post mortem examination showed, besides a cancer of the oesophagus without metastases, typical signs of hemorrhagic diathesis.

A survey of the literature made on account of the two cases showed that several authors had observed allergy-like reactions following roentgen treatment in the form of different kinds of exanthemas and urticaria. Some authors use the therme idiosyncrasis to roentgen rays, among them HOLTHUSEN (1), GUTZEIT (2), SOILAND (3), MAC KEE, TONSEY and FOVEUX DE COURMELLES (4).

Only in two papers I found reports on thrombocytopenia and hemorrhagic diathesis. EPSTEIN (5) (1925) described a case following roentgen treatment with extremely large doses for a cancer of the uterus to one anterior and one posterior field. DEN HOED, LEVIE and STRAUB (6) (1938) reported four cases of generalized malignant tumors, where teleroentgen treatment according to Mallet was given (*i. e.* great fields, including the whole trunk).

The fact that a thrombocytopenia and a hemorrhagic diathesis may result from teleroentgen therapy and from experimental irradiation of animals is stated by several authors. Even in roentgen treatment of blood diseases so called aleucia haemorrhagica has been recorded. On the other hand I have not observed any reports in the literature that a similar condition may appear in consequence of »ordinary» local roentgen treatment to relatively small fields, in patients with a relatively normal blood cell formula as in the two cases, that I have just described.

KORNBLUM, BOERNER and HENDERSON (7) (1938) have published a report of a very complete blood examination including thrombocyte count in 48 cases treated chiefly with roentgen in the ordinary ways. They stated that 35 patients showed a decrease and 13 an increase in the platelet count. They could not notice any clinical manifestations or hemorrhagic tendencies in connection with the reduction of the platelets and they found »no evidence that this reduction in the platelet count was of particular clinical significance.»

When comparing my own two cases with those found in the literature I got the idea that there might exist a similar but perhaps less pronounced effect of »ordinary» roentgen treatment. Hence in December 1945 I began an investigation of the effect of radiation on the thrombocytes and the blood clotting.

This investigation which so far concerns 40 patients has shown a definite reduction in the number of platelets in two thirds of the cases (examples see figs. 1 and 2), partly during the last week of the treatment or immediately after treatment, partly four to six weeks later. In some cases this late thrombocytopenia is more pronounced than the initial reduction. Five patients showed not only thrombocytopenia but also marked clinical manifestations of hemorrhagic diathesis. In two patients the cause of death must be ascribed to this hemorrhagic diathesis. A third patient when blood testing was done, showed an increase to one hour of the bleeding time. This case is very striking with regard to the relatively small roentgen doses, which were given to the whole vertebral columna.

Thus I have found that thrombocytopenia and a certain risk of hemorrhagic diatheses — even with fatal course — may follow even »ordinary» roentgen treatment, when fairly large doses are given. The effect of the thrombocytes and the mentioned risk of bleeding will on the whole be more marked the larger the doses and the greater the fields are.

The thrombocytopenia will most regularly appear, when radiation is given over thorax, perhaps especially sternum, and to the whole vertebral columna. Irradiation of the pelvis and the skull seems to be less dangerous from the mentioned point of view.

It seems to me to be of great importance to follow the thrombocyte curve when radiation is given in the above mentioned ways, especially at the end of the series of treatment and during the five or six weeks following treatment. Such a control of the thrombocytes may be of greater clinical value than the present control of the leukocytes. Of course the leukocyte count should not for that reason be abandoned.

It is obvious that therapeutical remedies should be tried in order to prevent radiation thrombocytopenia. Such an investigation will be carried out as soon as I get better possibilities to study the whole clotting mechanism of radiated patients. I am especially thinking of liver extracts, vitamins such as b, c and k. Nuclein acid is also said to be used with a certain success in malignant granulocytopenia.

Because of technical difficulties I have hitherto mainly been able to follow the blood platelet count. In a few cases — they are all too few for conclusions — I have had the opportunity to examine the clotting time and the clotting retraction. In the future I intend to study the different factors of the clotting mechanism with the aim of finding out, if any other disturbances than reduction of platelets and increase of

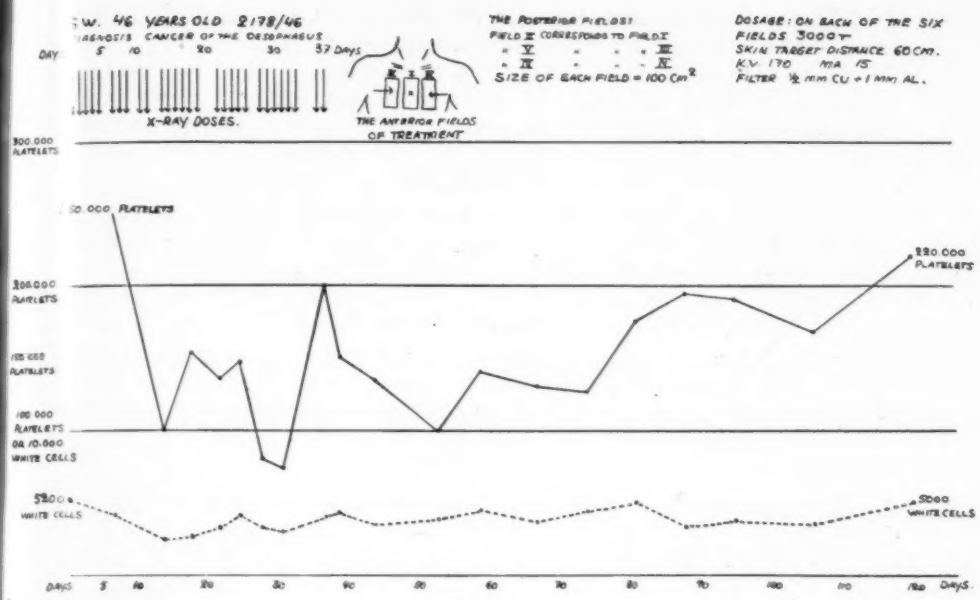
W. 46 YEARS OLD 2178/46
DIAGNOSIS CANCER OF THE OESOPHAGUS
DAY 5 10 20 30 37 DAYS
X-RAY DOSES.
THE ANTERIOR FIELDS OF TREATMENT
THE POSTERIOR FIELDS:
FIELD II CORRESPONDS TO FIELD I
" V " " " III
" IV " " " IV
SIZE OF EACH FIELD = 100 Cm²
DOSAGE: ON EACH OF THE SIX FIELDS 300 r
SKIN TARGET DISTANCE 60 Cm.
K.V. 170 MA 15
FILTER ½ mm CU + 1 mm AL.
300.000 PLATELETS
220.000 PLATELETS
200.000 PLATELETS
100 000 PLATELETS OR 10.000 WHITE CELLS
5000 WHITE CELLS
DAYS 5 10 20 30 40 50 60 70 80 90 100 110 120 DAYS.

Fig. 1.

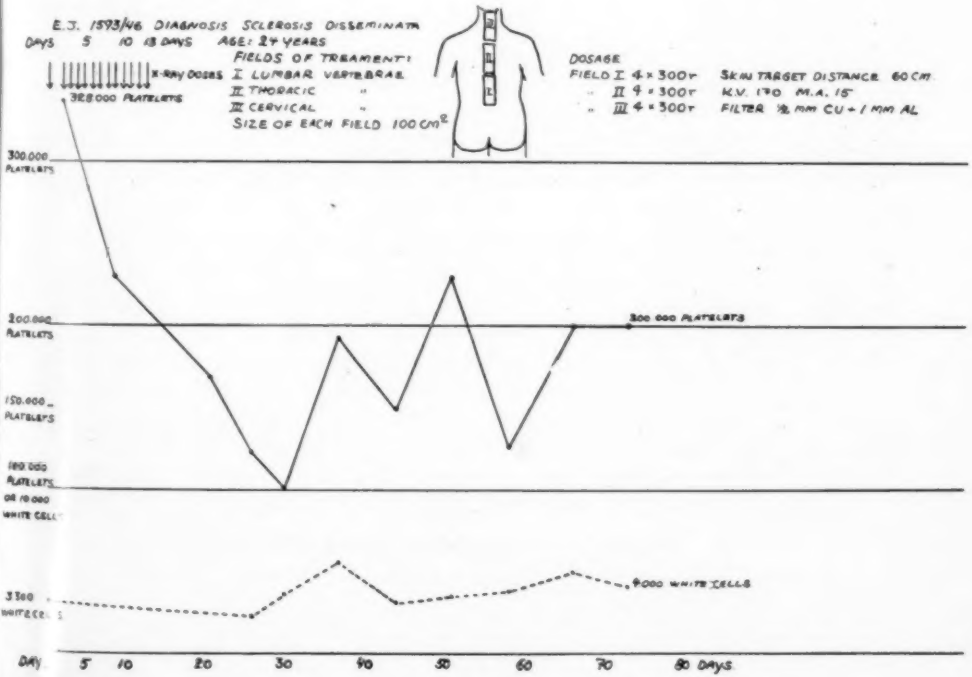
E.J. 1593/46 DIAGNOSIS SCLEROSIS DISSEMINATA
DAYS 5 10 18 DAYS AGE: 24 YEARS
FIELDS OF TREAMENT:
I LUMBAR VERTEBRAE
II THORACIC "
III CERVICAL "
SIZE OF EACH FIELD 100 Cm²
X-RAY DOSES
328.000 PLATELETS
DOSAGE
FIELD I 4 × 300 r
" II 4 × 300 r
" III 4 × 300 r
SKIN TARGET DISTANCE 60 Cm
K.V. 170 M.A. 15
FILTER ½ mm CU + 1 mm AL
300.000 PLATELETS
200.000 PLATELETS
300 000 PLATELETS
150.000 PLATELETS
100 000 PLATELETS OR 10 000 WHITE CELLS
3300 WHITE CELLS
9000 WHITE CELLS
DAY 5 10 20 30 40 50 60 70 80 DAYS

Fig. 2.

bleeding time as I have found in two cases, can be recorded. This investigation will also comprise patients treated with radium.

Finally the changes in the bone marrow will be studied as far as possible, partly those owing to local radiation effect, partly possible distant radiation effect on the marrow, outside the proper fields of treatment.

SUMMARY

The author has found a definite reduction in the platelet count in several patients treated with roentgen in the ordinary ways. The importance of following the thrombocyte count during and after roentgen treatment is stressed.

ZUSAMMENFASSUNG

Verf. hat bei mehreren in gewöhnlicher Weise mit Röntgenstrahlen behandelten Kranken eine entschiedene Abnahme der Blutplättchen gefunden. Die Bedeutung der Verfolgung der Thrombozytenzahl während und nach Röntgenbehandlung wird betont.

RÉSUMÉ

L'auteur a constaté une nette diminution du nombre des plaquettes sanguines chez plusieurs malades traités selon les techniques ordinaires par les Rayons Roentgen. Il souligne l'importance des numérations régulières des thrombocytes pendant et après le traitement par les Rayons Roentgen.

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ON SPONTANEOUS CHRONIC INTESTINAL INVAGINATION IN ADULTS[1]

by

P. Bjerre Hansen

Chronic invagination of spontaneous occurrence in adults is only rarely referred to, and as a perusal of the literature moreover seems to reveal somewhat varying perceptions in this domain, two such cases will be reported here which in 1944 were diagnosed at the Roentgen Department of »Centralsygehuset» at Randers (Denmark), and a brief account of the roentgenologic development in this domain will be given in that connection.

In both cases the roentgen examination was performed both by administration of a meal and an enema containing contrast medium. This procedure is not new, but the method does not seem to be so generally accepted as it deserves, for which reason it will be mentioned here and its advantages will be pointed out.

Moreover one of the cases reported shows that »roentgen disinvagination» may be completely successful, even in cases where the invagination has persisted for several weeks, and that it should therefore always be tried in such cases.

The first roentgenologic observation and description of an invagination was made by LEHMANN (1911, published in 1913) and it was just a subacute or chronic case in an adult. (Colicky abdominal pain for about 3 weeks — alternating diarrhoea and obstipation.) On studying roentgenograms after contrast medium enema LEHMANN found and described the typical »bicornate» invagination figure.

In 1915 GROEDEL and STIERLIN described roentgenograms of invagination, but the diagnosis was only established on operation. In 1919 ALTSCHUL diagnosed a case by means of roentgen examination. On operation the cause was found to be a sarcoma of the small intestine.

[1] Submitted for publication, Oct. 14, 1946.

In 1920 MUFF described a case of chronic invagination in an adul (abdominal pain for 3 months — slight obstipation — no blood in th stools — right abdominal mobile tumour) and called attention to a typic detail in the roentgen findings, namely a partial filling of the invaginatio sheath with contrast medium in the form of large broad rings or arche across the intussusceptum. This is partly due to the fact that the ape of the intussusceptum does not fill the lumen of the intussuscipien completely, partly to the fact that the colon ascendens and the coecu are shortened, which causes the haustrae to be closer to each other and deeper.

MUFF was of opinion that acute invagination required so early surgical interference that a roentgen diagnosis had to be dispensed with in such cases, roentgen examination being used only in chronic cases.

Moreover publications by LAURELL, 1922 and CZEPA, 1922 can be mentioned and by REGNIER, 1924, who described a fine peroral examination in which the intussusceptum, filled with contrast medium, is seen like a narrow stripe through the central part of the colon section containing the intussusceptum.

In this way the roentgenologic picture of the invagination, partly after contrast meal and partly after contrast enema, was gradually ascertained as far as the subacute and chronic cases are concerned.

Simultaneously a still brisker development of the roentgenologic diagnostics in acute invagination in children took place and in 1927, on the basis of the older method of reposition by means of fluid enema a. m. Monrad, the »Roentgen disinvagination» with contrast enema in connection with transillumination was introduced. REETAN (U. S. A.), POLIQUEN (France), and OLSSON and PALLIN (Sweden) prepared this technique independently of one another. From Denmark publications by HELSTED and ARNTZEN, JACOB NORDENTOFT, JACOBY and SVEN MÜLLER, and JENS NORDENTOFT can be mentioned. They only dealt with the acute invaginations in children all of them, and the good diagnostic and therapeutical results for a long time contributed towards directing the main interest to the cases of invagination in children, and at the same time a colon enema was to a great extent considered the only method of examination in adults, whose invaginations were partly neglected roentgenologically.

In 1932 RENANDER complains that there is only a very scanty literature on invaginations in adults and he blames the surgeons to some extent, as in his opinion they operate without sending the patient to roentgen examination. RENANDER himself describes the case of a woman, aged 49 years (abdominal pain for a fortnight — anorexia — emaciation — a mobile tumour, the size of a fist in the right hypochondrium), in which after enema the roentgenograms showed a typical invagination

f gure with the apex of the intussusceptum in the middle of the transverse c lon and the characteristic (»Muff's») arched contrast stripes round the i tussusceptum in the anal direction of the invagination figure itself. E xamination after peroral administration of contrast medium was tried b t without any real result. The operation revealed the case to be a stalky t mour from the valvula Bauhini.

The increasing experience and the spread of the knowledge of roentgen d agnostics and therapy of the invaginations of childhood have, however, o the other hand during recent years caused invaginations of adults also t be examined and the diagnosis to be verified more frequently by means o roentgen examination.

During recent years many casuistic and monographic communications have appeared, of which the following will be mentioned: LAURELL 1932 and 33, HOLMGREN 1938 and CLAUSEN 1944 (all 3 Sweden), PICCHIO 1938 and BONIMINI 1939 (Italy), SCHATZKI 1939 (U. S. A.) and RENÉ J. GILBERT and I. GARCIA-CALDERON 1944 (Switzerland).

The 2 latter authors very instructively reported an roentgen examination of a chronic invagination in an adult pt. both after contrast meal and contrast enema, revealing the invagination as well as the tumour causing it in this case.

According to the occurrence and duration of the symptoms invaginations may be divided into the following groups (according to DELANNOY among others):

1. acute
2. subacute
3. chronic a) recidivating; b) continual; c) intermittent.

1: Cases where the first attack sets on as an acute abdominal disorder with intestinal obstruction of rapid occurrence. These include almost all invaginations of childhood and they are spontaneous almost all of them.

2: Cases with acute onset but with a somewhat protracted course without marked intestinal obstruction. Occurs in children but is relatively most frequent in adults and is most frequently due to an organic alteration.

3 a: In these cases the invagination recurs, having been completely disinvaginated. Is not infrequent in children in this sense and rare in adults unless it is due to the fact that a possible organic cause has not been obviated.

3 b: Is characterized by a frequently rather acute onset, then passing on to a more persisting condition with several or few abdominal complaints, but with intestinal obstruction only after the course

of a long time. Is of common occurrence in adults; the etiology s varying.

3 c: In these cases sudden typical symptoms occur repeatedly, alwa s subsiding spontaneously. Rather typical of many cases due o tumours.

The cases reported in the following rather come under group 3), but the general clinic, mechanics and systematics will not be referred o here. Only the roentgenologic symptoms and the etiologic conditio s will be briefly mentioned.

The roentgenologic signs of invagination can be divided into two groups on the basis of the roentgen picture, partly after filling of the colon, partly after contrast meal. Only the conditions of the two great groups, invag. ileocoecalis and invag. ileocolica, will be referred to together with the differential diagnosis between them. The other groups will then hardly need any explanation.

A. After filling the colon: 1) The invag. figure
2) Dislocation of the colon.

1.

Invag. ileocoecalis	Invag. ileocolica.
a) Abrupt, smooth stop of the contrast column	a) — do —
b) »Bicornate» figure	b) — do —
c) Partial filling of the invagination sheath in arched or ring-shaped stripes, corresponding to the dilated »wrinkled» haustrae.	c) Less marked, but rather smooth filling along the wall of the colon, the haustrae not being »wrinkled».
d) Combination of b) and c).	d) — do —
e) Apparently complete filling of the colon, but with a central stripe-like clearing.	e) — do — but more frequent and more marked in most cases.
f) Contrast medium in the intussusceptum (very rare)	f) — do — (still rarer)
g) Gaseous dilatation of the terminal ileum coils reaching the coecal region.	g) — do —

2.

a) Right flexure depressed	a) b) and c)
b) Coecum drawn upwards	are not seen,

c	Centripetal curving and dilatation of affected part of colon, the centre corresponding to the middle of the mesenteric radix.	the coecum and the ascending colon are in situ.
B	After peroral administration of contrast medium:	
	Invag. ileocoecalis	Invag. ileocolica.
1)	Delayed intestinal passage	1) — do —
2)	Dilatation of the terminal ileum coils	2) — do —
3)	Beak-shaped stricture at the passage into the coecum	3) — do — more frequently relative than absolute stenosis.
a)	Stop at the ileocoecal juncture in the case of absolute stenosis.	
b)	Continuation as a narrow chord without peristalsis at the site of the coecum and the ascending colon. In both cases the ileocoecal part is displaced upwards corresponding to what is mentioned under A 2.	No displacement of the ileocoecal part.
4)	Partial filling of the invagination sheath in arched or ring-shaped stripes owing to retrograde passage (= A 1 c).	4) — do — but less marked.

As to the etiology of invagination the following groups can be set up:

A. Spontaneous invaginations, *i. e.* cryptogenetic without demonstrable organic cause.

B. Invaginations caused by demonstrable abnormal organic conditions in the intestinal section in question:

1) Tumours
2) Meckel's diverticulum
3) Ulcera, tuberculous, dysenteric etc.
4) Corpora aliena (including intestinal worms).
5) Appendicitis or its sequelae (adhesions etc.)
6) Developmental anomalies, *e. g.* consisting of a persisting mesenterium commune.
7) Various more indefinite conditions forming a borderland between the 2 main groups, *e. g.* hyperirritability (in enteritis, exaggerated

use of aperients etc.), traumata, abnormally large or swollen Peye 's patches etc.

Practically all invaginations in children come under Group A, a d most authors, surgeons as well as roentgenologists, are of opinion th t spontaneous invaginations practically do not occur in adults. The p e-dicate of cryptogenetic will, of course, always be considered complet ly dissatisfactory, and as to the spontaneous invagination the existence of less obvious etiologic factors than those referred to in Group B m st be supposed, for instance disturbances of innervation, or the like, which are not yet sufficiently known.

Almost all the individual cases of invagination in adults referred to above (LEHMANN, ALTSCHUL, MUFF, REGNIER, RENANDER, RENÉ J. GILBERT and GARCIA-CALDERON) were caused by abnormal organic conditions and when going through greater collective materials, both of recent and older date and by surgeons as well as by roentgenologists, very few cases of spontaneous invagination are found; nearly all cases are of organic causation, even if the distribution within the different groups is rather varying.

In this connection I just want to mention the classical surgical publications by ELIOT & CORSCADENS (1911) who, among 300 cases of invagination in adults, found intestinal ulcerations in the majority of the cases and tumors in 100 cases, 3 cases only being without demonstrable organic cause. KASEMEYER, too, found only 7 out of 284 cases without definite etiology, and in by far most of the cases be found tumours as the cause of the invagination, about 220 in all, 85 of them being malignant. In 42 cases a Meckel's diverticulum was found, whereas intestinal ulcerations were found in 15 cases only, 8 being tuberculous. Of publications of a more recent date EHNMARK's (1935) on invagination and tumours of the ileocoecal region will be mentioned. He finds 132 cases in the literature and reports 7 of his own cases of tumor ilecoecalis with invagination and believes to be able to demonstrate this combination in 4 or 5 out of 10 older cases of cancer ileocoecalis. EHNMARK concludes that invagination and tumour in adults are so closely associated, at any rate in the ileocoecal region, that if a tumour is found an invagination should be looked for, and reversely.

Invaginations of organic determination thus seem to constitute the great majority, but a Finnish surgical publication of 1935 by R. GULLICHSEN reports the case records of 234 cases of invagination, all of them verified on operation at a number of Finland's great hospitals. After a close examination of GULLICHSEN's material of case records, comprising patients at all ages, all invaginations in adults (*i. e.* pts. over 16 years) have been left out. The total is 126 cases which have been examined more closely with the following result:

	1) I. ileocoecal.	2) I. ileocolica.	3) I. colica.	4) I. jejunal.	5) I. coecal.	Total
+ Organic cause	2 (1 acute)	14 (1 acute)	2 (1 acute)	0	1 (0 acute)	= 19
— » »	49 (4 acute)	47 (5 acute)	7 (1 acute)	2 (1 acute)	2 acute	= 107

According to the case records the 19 organic causes were as follows:

1)	tumor coeci	1
	tumor ilei terminalis	1
2)	adhæsiones peritonæi	11
	diverticulum Meckeli	4
	carcinoma ilei	2
	sarcoma ilei	2
	tumor ileocoecalis	1
	polypus ilei	2
	lipoma ilei	1
	enterocystoma ilei	1
3)	lipoma coli	1
	cancer coli	1
4)	0	
5)	appendicitis gangrænosa	0

107 spontaneous cases as against 19 non-spontaneous is a figure that is quite contrary to the figures arrived at by the authors quoted above. There are relatively far more cases in adults (about 50 %) as against about 10 of most other authors), and among these there are rather many acute cases. The majority of the remaining 108 cases in children are acute in correspondence with the prevailing perception. The greater part of the case record material is, however, rather old, of about 1900 to about 1930, and it must be supposed that many cases of invagination in children, especially during the first 2 decades, have not come under treatment in the Finnish hospitals, as the material comprises a comparatively greater number of cases in children in the third decennium. This may explain the relatively great number of cases in adults, but it is impossible to give any explanation of the other contrasts. Invaginations without organic causation must doubtless be considered of not infrequent occurrence.

The 2 cases observed at the roentgenologic ward here and reported below must be considered to be spontaneous both of them and display rather uniform pictures. In the course of the same period invagination on organic basis has been diagnosed here in only 1 case, perhaps 2 cases.

I. A man, aged 29 years. In good health previously. About 5 weeks before admission at the end of Febr. 1944, suddenly ill with intense and diffuse abdominal pain. The pain subsided a little, but then remained fairly constant, often with aggravation after the meals and there was severe diarrhoea with several liquid somewhat mucous, non-hemorrhagic motions daily. Now and then vomiting a few times. Diet, rest in bed, tinct. thebaica at home without any effect. There was considerable loss of weight in the course of the 5 weeks.

On admission: Not exhausted, emaciated. The abdomen soft, a somewhat doubtful intumescence is felt in the right side of the abdomen. Still pain and diarrhoea coming on in attacks.

Laboratory examinations: Feces + benz., + mucus + catalase, no pathogenic intestinal bacteria. Test meals: Nothing abnormal. Urine and examination of the blood: Nothing abnormal.

On roentgen examination, partly after contrast enema, partly after peroral administration of contrast medium an invag. ileocoecal. is demonstrated, and after filling of the colon disinvagination at last proves successful. No roentgenologic signs of tumour.

The pt. was discharged in complete well-being.

II. A man, aged 35 years. Previously, in 1934, renal gravel and in 1939 gastric ulcer. No symptoms now from either of these disorders.

Was suddenly taken ill in July 1944 with epigastric pain coming on in attacks, vomiting once and one liquid motion + flatus. Is admitted for acute appendicitis and operated at once. On operation a long swollen appendix is found lying just inside but difficult to remove, as the basis is fixed and the coecum cannot be pulled out. The appendectomy is, however, successful and nothing is stated about invagination, either of the appendix or the coecum. The mucous membrane of the appendix is slightly swollen and red. The pt. is discharged 10 days after the operation.

7 or 8 days after discharge he is ill again with violent diarrhoea for 3 or 4 days and epigastric pain. The motions remained fluid and there was still slight pain in the epigastrium but otherwise no special complaints. The appetite was good, but still there was a considerable loss of weight, about 10 kg. in the course of 6 weeks.

Is admitted again in September 1944. Not especially emaciated. Liquid motions several times a day. Just above the umbilicus a transverse, sausage-shaped, rather big, slightly tender and somewhat mobile intumescence is felt, otherwise no special findings in the abdomen.

Laboratory examinations: Feces do not react to benzidin, 3 times.

Roentgen examination shows an invag. ileocoecalis, the reposition of which is only partially successful.

The pt. is therefore operated and an invag. ileocoecalis reaching about as far as the flexura lienalis is found. The disinvagination is fairly easily achieved, the last part of it is, however, rendered difficult by extensive adhesions between the surfaces of the intussuscipiens and the intussusceptum. The coecum is somewhat oedematous. No signs of tumour.

The pt. is discharged in complete well-being a fortnight later.

There can hardly be raised any objections against the spontaneity of the first case, but in the second case it cannot be excluded with absolute certainty that the appendicitis may have played a part; the question is, however, if there has been any real appendicitis. There are probably good reasons for the perception that it was a case of invagination all

t e time and the slight altera-
t ons of the appendix referred
t would then be secondary
a a consequence of the in-
v gination.

Roentgen examination
of Pt. No. I:

Fig. 1.

1) Roentgenograms after fi ing of the colon shows free p ssage to the coecum but w th defective filling of the la t 8 cm of the coecum a d the ascending colon with bl rred outlines of the bottom of the coecum. Perhaps the co cum is seen somewhat dislocated upwards. Immediately distal to the coecum a somewhat distended, gas-filled intestinal loop is seen passing from the coecum (Fig. 1).

The picture was perceived as suspicious of invag. and, after administration of contrast medium by the mouth, roentgen examination was therefore made again.

2) Roentgenograms after contrast medium by the mouth shows natural conditions of the stomach.

5 or 5½ hours p. c. filling of the upper part of the ascending and the transverse colon is seen, whereas corresponding to the coecum and the lower part of the ascending colon a central, fairly narrow contrast stripe is seen surrounded by the typical arched contrast stripes in the dilated and somewhat »wrinkled» coecum, which is also seen to be displaced a little upwards. The terminal ileum loops are seen to be dilated with an abrupt narrowing at the coecum, where the contrast medium continues distinctly in the narrow stripe in the coecum and the ascending colon referred to above (Fig. 2).

The examination is continued at once after renewed filling of the colon.

3) Now a distinct invagination figure is seen just at the flexura hepatica combined both with the arched stripes and the filling of the invaginated part of the small intestine produced by administration by the mouth (Fig. 3).

Fig. 2.

Fig. 3.

By increasing the pressure of filling to $1^1/_2$ m and by supporting manual reposition manipulations, disinvagination of the intestine and unfolding of the coecum were achieved (Figs. 4 and 5). Gradually it became impossible, however, to get a clear view as all the bowels were filled with contrast medium.

4) The next day renewed roentgen examination was made after filling of the colon (the bowels having been emptied) and quite natural conditions were now found.

Roentgen examination of Pt. No. II:

1) After barium enema the colon is seen to be normally filled to the flexura lienalis, but just at the passage into the transverse colon a complete stop with typically »bicornate» invagination figure is seen (Fig. 6).

The diagnosis was safe but in order to complete the examination contrast medium was administered by the mouth.

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 7.

Fig. 8.

2) Roentgenograms after contrast medium by the mouth, 6 hours p. c., shows a number of dilated intestinal loops in the pelvis minor, and towards the coecal region they are seen to end in a beak-shaped contraction from which two fine contrast stripes pass into the coecal region, where they pass on to 2 or 3 short, somewhat more filled intestinal loops situated at the site of the coecum. No contrast is seen in the colon (Fig. 7).

The presence of intestinal loops in the colon thus seems to have been proved.

3) On renewed filling of the colon the invagination is replaced in part, the intussusceptum being taken to the coecal region again, where a great defective filling still remains. The coecum itself is filled but there is no passage to the small intestine (Fig. 8).

The pt. was then operated as described above.

Epicrisis

The cases are reported of 2 patients, aged 29 and 35 years respe - tively, whose diseases are both characterized by acute onset with inten : but indefinite, diffuse abdominal, passing on to a chronic condition wi :

periodical, abdominal pain and diarrhoea with liquid, mucous, non-hemorrhagic motions and considerable emaciation.

Invaginatio ileocoecalis is demonstrated in both patients by roentgen examination which is performed both after a contrast meal and after filling of the colon with contrast medium.

In one case complete disinvagination, by means of contrast enema is achieved, in the second case only partial reposition can be carried through in this manner but is then performed in operation.

Both pts. live and have not displayed any symptoms since.

An organic cause is not demonstrated in any one of these cases by roentgen examination or on operation in one case, for which reason both cases are considered to be of spontaneous occurrence.

SUMMARY

After a brief account of the development of the roentgenologic diagnostics of intestinal invaginations, particularly with a view to chronic cases in adults, roentgenologic symptoms of invagination are explained. Peroral administration of contrast medium is pointed out as a method of examination in addition to, and combined with, the commoner contrast enema. The etiological conditions of the invaginations are discussed, and it is pointed out that spontaneous cases can scarcely be very rare, and this applies also to adults. Finally two cases of chronic spontaneous invaginations in adults are reported. The case histories are rather uniform and characteristic, and it is demonstrated that »roentgen disinvagination» may be successful even in these chronic cases, and should therefore be attempted.

ZUSAMMENFASSUNG

Nach einem kurzen Bericht über die Entwicklung der Röntgendiagnostik der Darminvaginationen, besonders im Hinblick auf chronische Fälle bei Erwachsenen, werden die röntgenologischen Symptome der Invagination erklärt. Es wird auf perorale Zufuhr von Kontrastmittel hingewiesen, als eine den gewöhnlicheren Kontrasteinlauf vervollständigende, mit diesem zu kombinierende Untersuchungsmethode. Die ätiologischen Verhältnisse der Invagination werden besprochen, und es wird darauf aufmerksam gemacht, dass spontane Fälle wohl kaum sehr selten sein können, was auch für Erwachsene gilt. Schliesslich wird über zwei Fälle von chronischer spontaner Invagination bei Erwachsenen berichtet. Die Krankengeschichten sind recht gleichförmig und charakteristisch, und es wird gezeigt, dass »Röntgen-Disinvagination» auch bei diesen chronischen Fällen Erfolg haben kann und deshalb versucht werden soll.

RÉSUMÉ

Après une courte revue consacrée au développement du diagnostic radiologique des invaginations intestinales, où il s'attache particulièrement aux cas chroniques chez les adultes, l'auteur délimite les symptomes radiologiques des intussusceptions. Il souligne l'utilité diagnostique de l'administration de substance de contraste par la bouche concurremment et en combinaison avec le lavement baryté, plus courant. Il discute des fac-

teurs étiologiques et fait ressortir que les cas spontanés ne doivent pas être tout à fait rares, pas même chez les adultes. Pour finir il rapporte, observés chez ceux-ci, deux cas d'invagination chronique spontanée. Les observations en sont très comparables et caractéristiques, et l'auteur fait voir que la désinvagination radiologique peut réussir même dans ces cas chroniques et mérite donc d'être essayée.

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FROM THE ROENTGEN DEPARTMENT OF THE SWEDISH RED CROSS HOSPITAL NEAR OSLO, NORWAY (CHIEF: TORFINN DENSTAD, M. D.)

HYPEROSTOSIS CRANII[1]

by

Torfinn Denstad, M. D.

Of the cranial hyperostoses it is first of all the diffuse form that captures interest and that will be discussed in the following. In the case of a patient in whom roentgen examination has disclosed such diffuse hyperostosis localised to the skull, the first question will be: Is a meningioma responsible for the thickening of the bone? Everything possible should be done to answer the question, because this is decisive to the mode of treatment. Already in 1907 SPILLER pronounced: »A local thickening of the skull is probably caused by a dural endothelioma.» Later, and especially in course of the 2 last decennia, many workers have appeared giving clear evidence of the frequency with which, particularly basal, often flat meningiomas (»méningéome en plaques»), are attendant on hyperostosis. Here I shall only mention works by CUSHING (1938), KORNBLOM (1935), ERDHEIM (1937), from Sweden by OLIVECRONA (1934), LINDBLOM (1936), ERIKSON (1936) and LYSHOLM and his collaborators (1937), and from Denmark by SØRENSEN (1937).

However, a diffuse thickening of the bones of the skull may also be seen in other conditions, especially as part of a systemic disease. It may be seen in osteitis deformans Paget, Albers-Schønberg's disease, hyperparathyroidism and in lymphogranulomatosis. Further in cancer metastases, leukemia, some forms of anemia and in tertiary lues. In polyostotic fibrous dysplasia (JAFFE and LICHTENSTEIN) there may also be unilateral cranial sclerosis.

The clues to the differential diagnostic of these various sufferings will not be entered upon. A careful clinical and roentgenological examination will in the great majority of cases disclose the true nature of the disease.

There is one condition, however, that is not so easily done with, namely the so-called idiopathic diffuse hyperostosis of the skull. The

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problem here is whether the condition at all exists as a separate morbid picture.

Already in 1697 MALPIGHI reported a case of cranial sclerosis. DANIËLS, who in 1883 gave a detailed description of such a case, mentions a total of 13 earlier described cases. Quite naturally most reports from this preroentgenologic period derive from anatomical collections and museums, and there is reason to presume the material to be somewhat heterogeneous.

In his discourses on pathology VIRCHOW (1863—65) introduced the concept of leontiasis ossea faciei, a purely descriptive designation. The term is objectionable, because too much it directs attention to the sometimes considerable enlargement of the upper and lower jaw. It has further led to mention of symptomatical forms of leontiasis ossea, particularly in osteitis deformans and osteitis fibrosa generalisata (GEMMELL, 1935, SVÁB 1937, KIENBÖCK 1940—41, TROLLE 1942), but also in lues (SCHARFF 1936), neurofibromatosis etc. Thus KIENBÖCK recognises only 5 of the earlier described leontiasis ossea as »true» cases.

For the rest some authors believe leontiasis ossea to be nothing but a localised form of osteitis deformans or osteitis fibrosa generalisata, because of similarity of the histological pictures (FREEDMAN), others that the three sufferings represent clinical forms of the identical disease (LANGENSKIÖLD 1921, REISS 1936). However, LANGENSKIÖLD's work dates back to the time before MANDL in 1925 pointed out hyperparathyroidism as a separate morbid picture. All told, one should be very careful from microscopical likeness to conclude identical etiology or pathogenesis.

In the great majority of cases described as idiopathic hyperostosis, cranial sclerosis or leontiasis ossea, more or less defined osteomas or fibro-osteomas have been shown in bones of the face, occasionally combined with a more diffuse thickening of adjacent bones. Those are clear cases. But in less advanced cases with only a diffuse thickening of the skull, most often localised to anterior or middle cranial fossa, there can be a little doubt as to whether a meningioma is lurking back of the hyperostosis. And in the cases of this kind that I have seen reported, has this possibility never been altogether eliminated.

I shall report 3 cases in which one has been faced with these differential-diagnostical problems.

Case No. 1: A woman of 67 years was admitted $^{25}/_{10}$ 1944 to the medical department of the Swedish Red Cross Hospital (Pt. No. 1362/44), because for 8 years she had been suffering from an increasing dizziness. In course of the last months also severe tremor of left hand had appeared, and her facial expression had become stiff. The neurologic examination revealed reactions indicating a lesion centrally in right and probably

Fig. 1.

Fig. 2.

Fig. 1. Case 1. Sclerosis supraorbitally and of proc. frontalis ossis zygomatici on right side. Also hyperotosis frontalis interna.
Fig. 2. Case 1. Sclerosis of the base of anterior cranial fossa.

also in left hemisphere, most probably due to paralysis agitans, at present under the picture of hemiparkinsonism (LEIF EMBLEM).

Roentgen examination (Figs 1—2): In right frontal bone there is a sclerotic process, specially localised supraorbitally and posteriorly at the base of anterior cranial fossa, corresponding to the orbital roof. The sclerosis also spreads to proc. frontalis ossis zygomatici. Upward in the frontal region on both sides of the middle line also minor hyperostoses are seen, separated from the described sclerosis, presenting the typical picture of hyperostosis frontalis interna.

On *encephalography*, in which good filling of the ventricle system as well as of the basal cisterns was obtained, somewhat wide ventricles were found, but not more than normal at her age. Further slight asymmetry of the anterior horns was seen, the right anterior horn not being quite as broad as the left one. However, it is not deformed nor dislocated, and in a lateral view, resting on back of the head, they completely cover one another.

Unfortunately angiography was not made. However, this examination is of minor importance to the question of subfrontal tumors (ARNE ENGESET). Roentgen examination of rest of the skeleton revealed nothing of special interest. W. R. negative.

Case No. 2: A woman, 40 years of age, was $^{19}/_{6}$ 1944 admitted to the Swedish Red Cross Hospital (Pt. No. 422/44). For well over 3 years she had had severe pain in left cheek, partly a persistent ache, partly violent attacks radiating to the ear, forehead and chin.

In the spring 1943 she was staying at the neurologic department of the University Hospital (Pt. No. 1079/43). The left pupil was found slightly smaller than the right one, there was deviation of the jaw to the left, slight hypoesthesia of left upper lip, and slight paresis for lifting of left corner of the mouth.

In 1942 an unsuccessful attempt had been made at dividing 2nd trigeminal branch. This operation was now repeated twice with no effect on the pain (ARNE TORKILDSEN). There was no sign of a meningioma. W. R. was negative.

Fig. 3. Case 2. Sclerosis of the sphenoidal wings and of the ethmoidal cell-region on left side.

Roentgen examination $^{20}/_{2}$ 1943 (Figs 3—5): Sclerosis of great and small sphenoidal wing on left side, possibly also of corpus ossis sphenoidalis — at least, the sinus is invisible. The sclerosis further extends to os zygomaticum with the arcus, that is thickened, and to the posterior ethmoidal cells, where the cells are replaced by compact bone. Foramen ovale is possibly slightly narrower on left than on right side. There is also calcification of the choroid plexus, that is in its usual location, and of falx.

At the Swedish Red Cross Hospital *encephalography* was made. Good filling was obtained of the anterior and temporal horns, and scarce of 3rd ventricle, no abnormality was demonstrable. Later ($^{7}/_{3}$ 1945) also *arteriography* was made. Good filling of art. cerebri ant. and of art. cerebri media with ramifications was obtained. Roentgenograms in two planes were taken, and appeared normal.

It should be added that the patient 24 years earlier, at the age of 16, had been operated for a large bone-hard tumor in left upper jaw (Professor PETER BULL). The tumor had filled the entire maxillary antrum, and had also invaded the pterygoid process and extended upward to base of the skull. Histologic diagnosis: Fibro-osteoma (Prof. FRANCIS HARBITZ).

Fig. 4. Case 2. Sclerosis of the base of middle cranial fossa. Sinus sphenoidalis is filled with compact bone. Operational defect in temporal region.

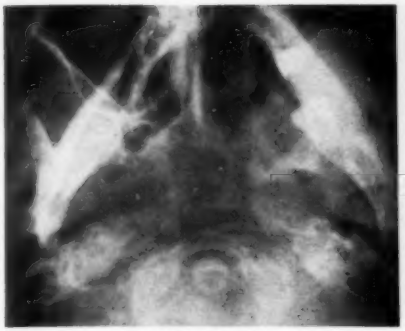

Fig. 5.

Fig. 6.

Fig. 5. Case 2. Distribution of the sclerosis in base of the skull is seen, as well as compact bone in posterior region of the ethmoidal cells.

Fig. 6. Case 3. Sclerosis of the sphenoidal wings, the zygomatic arch and region of the ethmoidal cells on right side.

Case No. 3[1]: A 67-year-old woman was admitted to the Swedish Red Cross Hospital on $^{12}/_{3}$ 1945 (Pt. No. 461/45). For 20 years she has had exophthalmos on right side that has not increased mentionably. Vision has been reduced to counting of fingers at 2 meters, and on ophthalmoscopy an atrophic, pale papilla was found. There was absolute central scotoma for all colour qualities but white. Further there was reduced audition of the conduction type on right side, deviation of raphe to the right and of the tongue to the left. The phosphatase content in the blood was 1.96 Bodansky units. W. R. negative.

Roentgen examination in 1938 (Drammen Hospital), 1939 (University Hospital, figs. 6—8) and this time (Swedish Red Cross Hospital) showed the same changes. Roof of the skull is somewhat thick. Particularly on the right side there are broad diploetic veins, considerable sclerosis of basis cranii on right side, specially localised to the sphenoidal wings, less to corpus itself, and further to clivus and posterior cranial fossa and to the temporal bone, where pneumatisation in the mastoid process is hardly detectable. Anteriorly the sclerosis spreads to the orbital roof, the ethmoidal and zygomatic bones. The affected bones are partly thickened, especially the lateral orbital wall, with consequent considerable narrowing of orbita. Because of the thickened walls is the sphenoidal sinus hardly visible. Corresponding to the posterior ethmoidal cells on the right side it is further seen a sharply outlined, dense bony area, the size of a hazel-nut and the appearance of an osteoma. There is also slight thickening of posterior part of the hard palate.

Encephalography was made, but only sparing filling of left lateral ventricle was obtained, very scarce of the right one, no certain filling of 3rd and 4th ventricle. Nor were the temporal horns demonstrable. Septum pellucidum is in the middle line, and there is no deformation nor dislocation of anterior part of the anterior horns. Appearance of the basal cisterns is normal.

[1] This case has already been recorded in »Norsk Forening for Medicinsk Radiolog» (1939).

Fig. 7. Case 3. Sclerosis of base of anterior and middle cranial fossae. Slight thickening of posterior part of the hard palate. Wide diploetic veins.

Angiography was then made. The frontal picture was unsuccessful (taken too early). The lateral view showed good filling of contrast in art. cerebri ant. and pericalosa and of the vessels of the Sylvian group. These are of usual appearance. There is also filling of art. temporalis superficialis.

Roentgen examination of the long bones gave no pathological findings.

Fig. 8. Case. 3. Shows distribution of the sclerosis also to posterior cranial fossa and the temporal bone on right side, as well as thickening of lateral orbital wall and osteoma formation in the posterior ethmoidal cells.

Confronted with the problem of whether a meningioma may be the cause of the described cranial hyperostosis, the following conditions have to be considered:

Whereas the convexity meningiomas often cause a mixture of destructive and proliferative osseous changes, accompanied by typical vascular changes, the basal meningiomas most often release only proliferative changes in form of hyperostosis and sclerosis. And these changes may be found extending over a region far exceeding distribution of the meningiom

itself. Cases have also been described in which the tumor penetrates into fossa zygomatica, or via fossa pterygoidea invades sinus maxillaris (CUSHING). The possibility of changes in the facial bones must also be counted on. The favourite location of the basal meningiomas further is just the region around the sphenoidal wings and the anterior cranial fossa around the olfactory nerve and over the orbital roof. In other words, they are capable of producing changes of the bones similar in appearance and location to those seen in the demonstrated cases. To this it comes that they often spread flatly »like a lawn», and several years may pass before they render any symptom. CUSHING has thus described the case of a woman, 73 years old, whose only symptom was an exophthalmos, slowly increasing in the course of 31 years.

Based on the symptoms and on the described cranial changes the presence of a meningioma cannot without further ceremony be excluded. EINAR SØRENSEN (1937) thus in his detailed monography claims basal hyperostosis to be pathognomonic to meningioma, even when occurring isolated, the simple osteoma occurring as a more well-defined tumor. Also ERIKSON (1936) shows great reserve regarding the occurrence of idiopathic hyperostosis in this location.

On the other hand, arguments of weight may be carried against the diagnosis of meningioma. Then I am first of all thinking of the normal encephalograms, and for 2nd and 3rd case, of the normal arteriograms. Even so, the presence of a flat meningioma may be suspected. This theoretical possibility can only be eliminated by an operation or in eventual autopsy. However, according to our experience, if based on a meningioma, dislocations and deformations of the ventricular system would be expected in such wide-spread bony changes, as pronounced as to be demonstrable even on scarce filling with air. And likewise changes in the angiograms. Here I shall recall to mind ERIKSON's examinations of meningiomas of the sphenoidal wings, in which in all cases there were dislocation and deformation of the ventricular system, or dislocation of the pineal body.

In the 2 last mentioned cases it was further shown compact bone in the posterior part of the ethmoidal sinus, interpretable as small osteomas. These changes are considerably more in agreement with an idiopathic hyperostosis than with a meningioma. Patient No. 2 had also earlier been operated for a fibro-osteoma in the upper jaw. In spite of the 21 years interval of no symptoms it seems reasonable to suspect a correlation between these two sufferings. And in the 3rd patient an osteoma was demonstrated proceeding from the hard palate. As a general rule one should in such cases of diffuse hyperostosis specially look for simultaneous presence of osteomas, particularly in the sinuses, as these may be differential-diagnostically significant.

In none of the three cases were bone or vascular channel change, pathognomonic to meningioma demonstrable, nor was there atrophy nor erosion of dorsum sellae. In the 3rd case the diploic channels were dilated, but this has possibly been due to obstructed outlet because of the hyperostosis.

Neither do the anamnetic informations and neurological findings offer direct indications of a cerebral tumor. In case No. 1 I feel inclined to consider the hyperostosis a finding of secondary importance, unconnected with the hemiparkinsonism. In the 2nd case is genesis of the pain rather baffling, persisting after nearly complete section of 2nd trigeminal root. Diagnosis from the neurologic department (the University Hospital) was that of atypic trigeminal neuralgia, but the possibility of sympathalgia or a functional condition has also been ventilated. And in the 3rd case the described symptoms may be attributable to pressure on the respective cerebral nerves, where they pass basis cranii, and deafness to the pronounced sclerosis of the temporal bone. Her exophthalmos is naturally due to the hyperostosis of the orbital walls, but it should be kept in mind that unilateral exophthalmos also is a very frequent symptom in basal meningioma (CUSHING, BERNSTEIN). However, in these latter the exopthalmos will as a rule be progressive, and not as in the present case remain stationary for 20 years.

It is further noticed that none of the patients have complained of headache, a symptom that usually, if not always, is very marked in meningioma.

On the whole, I believe the here mentioned cases to represent so-called idiopathic cranial hyperostosis, and I have considered demonstration of the cases justified in order to show that *such diffuse cranial hyperostosis is not pathognomonic to meningioma.* Also, again I shall take advantage of this opportunity to emphasise the necessity of, in such cases, to use all diagnostical means to eliminate the possibility hereof.

Otherwise, the here mentioned cases give rise to a few reflections, that here only will be touched upon, the material being too small for general conclusions.

LANGENSKIÖLD claimed osteitis fibrosa generalisata, osteitis deformans, leontiasis ossea and the central maxillary fibromas to be clinical forms of the identical suffering. Regarding leontiasis ossea or diffuse cranial hyperostosis and the fibro-osteomas, not rarely seen in the accessory sinuses, I believe he is right. The 2 last of my cases tell in favour of this theory. There is hardly reason to differentiate between a diffuse and a tumorous form, such as made by KNAGGS, nor between a form due to chronic periostitis and one originating with diffuse osteitis.

At any rate, the usual unilateral location directs attention to the polyostotic fibrous dysplasia, in which, as mentioned, similar cranial

c anges may be seen. Most often women are attacked, also the here mentioned patients were females. However, there were no other skeletal changes in support of this diagnosis. Also chondrodysplasia, Ollier's disease, is unilateral, but this is localised to cartilage-performed bones only.[1]

SUMMARY

The author describes an idiopathic unilateral diffuse hyperostosis of the skull in three elderly women. The affection occupies particularly the sphenoidal wings and floor of the anterior cranial fossa, but invades also the facial bones with osteoma-formation in the sinuses. The roentgenologic pictures resemble the ones seen in basal meningiomas.

ZUSAMMENFASSUNG

Verf. beschreibt eine idiopathische halbseitig lokalisierte diffuse Hyperostose des Schädels bei drei älteren Frauen. Die Affektion nimmt insbesondere die Keilbeinflügel und der Boden der vorderen Schädelgrube ein, greift aber auch auf die Gesichtsknochen über, mit Osteombildung in den Nebenhöhlen. Das röntgenologische Bild zeigt Ähnlichkeit mit demjenigen, welches man bei basalen Meningeomen sehen kann.

RÉSUMÉ

L'auteur décrit une hypérostose diffusée unilatérale idiopathique du crâne, chez trois femmes âgées. L'affection s'étend particulièrement aux ailes du sphénoïde et à la base de la fosse frontale, mais s'attaque aussi aux os de la face, avec formation d'ostéomes dans les sinus. La radiographie présente une image semblable à celle des méningiomes de la base.

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[1] In Acta Radiologica (1946, 27, 129) it has recently been published a work by Billing and Ringertz on fibro-osteoma, with 24 cases localised to the skull and 1 to a rib. Nearly all cases had been histologically examined. In 3 of the cases there was diffuse fibro-osteomatosis with essential location to the maxillary, zygomatic and sphenoid bones, markedly unilaterally. It is noticed that these patients were females. Pathogenetically the authors believe in the presence of osseous formation on basis of connective tissue, in various stages of advancement, a reproduction of the embryonal process, and they regard the affection mostly as an increasing malformation.

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CHANGES IN THE LUNGS IN 126 CASES OF ASBESTOSIS OBSERVED IN FINLAND[1]

by

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Helsingfors.

Asbestosis is a special form of pneumoconiosis caused by the inhalation of asbestos dust. This occupational disease, which is closely related to silicosis, has up to the present not to any note-worthy extent been observed in Scandinavia. So far as is known, only 5 cases, all from Norway, have been published (WOLFF, SCHRUMPFF and SCHIÖTZ). From Sweden and Denmark there are no reports as to asbestosis. It therefore appears well warranted to give an account of 126 cases of this serious, highly disabling and even mortal disease, all showing clear, roentgenologically demonstrable changes in the lungs of the patients.

The use of asbestos for technical purposes has rapidly expanded of late and will still further increase. Asbestosis naturally occurs mainly in countries where asbestos finds are worked and where there are domestic asbestos industries. But also in those countries where asbestos is not found and where the asbestos industries work with imported raw material, cases of asbestosis will be found to occur during the working up of the raw material. There is therefore all the more reason for the spreading of a more general knowledge of the dominant form in which asbestosis manifests itself, *viz.*, changes in the lungs, which »*in vivo*» are only differential-diagnostically demonstrable by means of a roentgenogram.

First of all some short data relating to the history, pathogenesis and clinique of asbestosis will be given. In medical literature the disease was for the first time described by MURRAY (cit. WOLFF) in 1900. Asbestosis has, however, most certainly occurred as far back in history as asbestos

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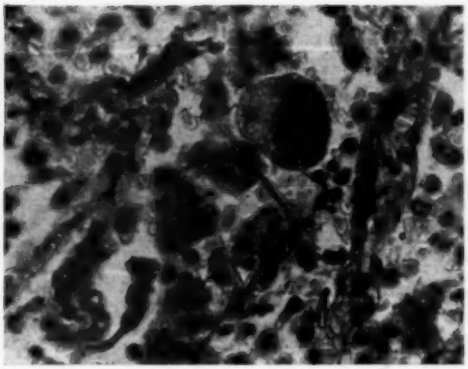

Fig. 1. The asbestos needles have caused an exudate infiltration in the lung tissue, in which also a few giant cells are found.

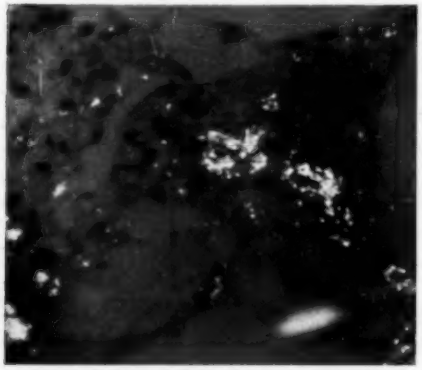

Fig. 2. The epithelium of the alveoli has noticeably thickened. (Picture taken in polarized light.)

mineral has been handled, *i. e.* for thousands of years. We have definite proof that the old Egyptians made use of asbestos for textiles which were intended to meet specially high demands on their wearing qualities. At present the mineral asbestos is used within wide branches of industry, *i. a.* as an excellent heat resisting and acid proof and also electrically insensitive insulating material. The largest known and worked occurrences of asbestos in the world are found in Canada, USA, Russia, South Africa, Finland and Italy. More than 50,000 persons are at present computed to be employed in asbestos industries in which it is possible for cases of asbestosis to occur. A collocation of all known cases of asbestosis is not available at present. From the Anglo-Saxon countries there are reports of in all almost 2,000 cases (LANZA, MEREWETHER and SCHULL). From Germany, where this industry is compelled to use imported raw material, accounts of about 400 cases have been published, mainly by SAUPE and WEDLER. The number of known deaths in asbestosis amounts to about 100.

The name asbestos is used to denote a number of mutually related magnesium silicates, containing variable amounts of iron, lime, water and bound silicic acid and with corresponding varying physical properties, such as strength, flexibility, etc. The crystals of asbestos have a typical fibrous structure. They are long, narrow and sharp, with a mean length of 20—75 μ and a thickness of 0.5—2 μ. In the course of the mechanical dressing which the industrial utilization of the

asbestos mineral mostly necessitates, dust heavily laden with crystals is generated. This is inhaled by the asbestos worker and the needles thus enter the finer airways of the lungs. The longer needles, which owing to their size cannot pass as far as to the alveoli, stop in the bronchioli, filling same up. In contrast to this, sharp, shorter needles can penetrate the parenchyma and are to be found also outside the bronchioli. In advanced cases of asbestosis these crystals are found in the lung tissue in such extraordinarily abundant quantities, that, according to BEGER, as many as 1.3 million asbestos needles have been found in 1 ccm volume thereof.

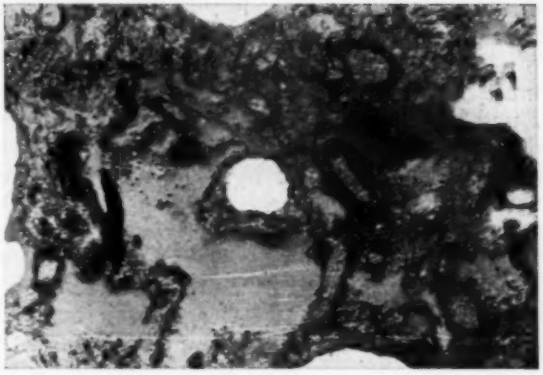

Fig. 3. Diffusive interstitial connective tissue formation in the lungs.

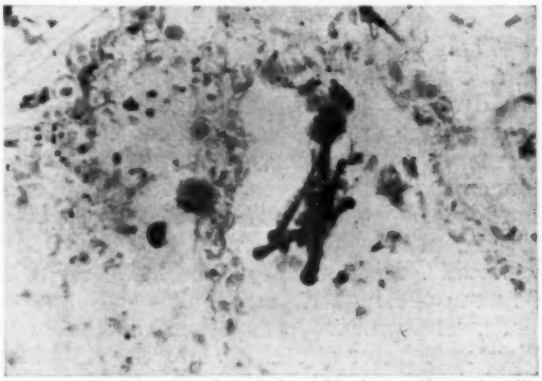

Fig. 4. Disintegrating asbestos bodies.

Contrary to what is the case in silicosis, the dust particles, which enter the lungs as »foreign bodies» are not phagocyted, nor are they carried away in the lymphatic channels. Instead, the asbestos needles are fixed in place through fibroblast-proliferation and reticularly arranged, peribronchial, fibrillous connective tissue. The fibrosis in its turn leads to disseminated shrivelling, the formation of so-called »asbestos corns» and local emphysema. Thus, while silicosis is a »parenchymatous, nodular fibrosis», asbestosis is a »diffuse, interstitial peribronchiolitic fibrosis» (WOLFF). Further, it should be observed that asbestosis mainly affects the basal and lateral parts of the lungs (probably owing to their greater mobility and the greater mechanical irritation caused thereby) while silicosis is especially localized in the more

central parts. Secondarily, more or less developed irritations of the pleura, in the shape of thickenings or adhesions, are common.

Among the pathological-anatomical criteria of asbestosis mention must finally be made of the curious bodies, known as »asbestosis bodies», found both in the lung tissue and in the expectorations. These are often dumbbell-shaped or are segmented and consist of an asbestos needle as a nucleus, surrounded by a gelatinous coating. Different schools of thought have not arrived at an agreement with regard to their etiology in the shape of mechanical tissue lesions or chemical irritation. The pathological anatomical preparations reproduced in the text have been more closely analyzed by NORO, with whom I have also enjoyed fruitful co-operation as regards the clinical investigations into my asbestosis cases. NORO joins himself more closely to the thought of the dominance of the phase of mechanical irritation, such as this was first expressed by the Swedes SUNDIUS and BYGDEN. The establishing of the occurrence of »asbestosis bodies» is not pathognomic as regards asbestosis, but shows that the patient in question has been exposed to the inhalation of asbestos dust.

The *symptomatology* of asbestosis is dominated — as is also the case in silicosis — by dyspnoea and an irritating cough. In most instances the dyspnoea is due to secondary emphysema. In the more advanced stages there are also disturbances of circulation, due to the increased resistance in the lungs; hypertrophy of the right side of the heart is found in varying degree. The irritation of the cough is usually greatest in the mornings, there is *little* or no expectoration. Conjunctivitis, laryngitis and pharyngitis are frequently observed as ante-primary stages of asbestosis. *Diagnostically* remarkable is in earlier stages the contrast between the high degree of dyspnoea and the paucity of the clinical finds. The positive occupational anamnesis is naturally a differential diagnostic factor of decisive importance. As far as diagnosis is concerned one is in other respects compelled to have recourse to roentgen examination of the lungs, which will be dealt with more particularly in a later section of this paper.

Disturbances of circulation and intercurrent infections in the weakened respiratory organs are foremost among the *complications* arising. The heart insufficiency is the factor which in more advanced cases is most frequently the immediate cause of death. Bronchiectasises and bronchopneumonies with strikingly grave prognosis are further common secondary complications in asbestosis. Exudative pleurisies seldom occur, while, on the other hand, different kinds of thickenings of the pleura are very common. As regards the combination of tuberculosis of the lungs and asbestosis there are contradictory reports. Of late especially the Anglo-Saxons (MEREWETHER) have — based on statistics —

maintained that tuberculosis does not occur more frequently among asbestos-workers than within other groups of industrial workers. According to certain reports in literature, a combination with carcinoma (NORDMANN, cit. SAUPE) is conceivable. Most authors consider the *prognosis* to be markedly unfavourable, with a decidedly greater tendency towards progression than is the case in silicosis. In statistical compilations by MEREWETHER and BRIDGES (cit. WOLFF) based on a great deal of material, the average length of life during exposure to asbestosis-engendering work is given as 15.2 and 12.4 years respectively, as against 40.1 and 35.1 years respectively in silicosis-inducing work. This and other statistical material stands in direct contradiction to SCHRUMPF's assumption of a »still more gradual development» of asbestosis than of silicosis. The interval of time before the manifestation of asbestosis during continued exposure is given with great variations. MEREWETHER thus reckons with an exposure of about 7 years, whereas SAUPE in unfavourable cases has found manifest asbestosis already after an exposure of 9—10 months. In this respect, as is the case also in silicosis, a number of variable factors such as individual susceptibility and the massiveness of the asbestos dust naturally play a great rôle and give scope for very great breadth of variation.

The Occurrence of Asbestosis in Finland

My material embraces 126 roentgenologically manifest cases of asbestosis among 476 workers, all employed by the firm Finska Mineral A.B. The roentgen examinations of these workers, more particularly discussed below, have been carried out on the initiative of Medical Councillor LAVONIUS, the Chief Physician of the respective Insurance Company. Of the 126 workers affected by asbestosis 34 are employed in the Company's dressing works at the mine in *Paakkila* (north-eastern Savolax), while 92 are working in the factory for finished products near Helsingfors. While due heed has been paid to the positive occupational anamnesis, the diagnosis has been made on the basis of the roentgen findings. Further particulars as to this will be given in the following section, where the results of the roentgenological classification have been tabulated. In most cases the photographing has been repeated once a year during the past three years. The roentgen diagnosis in each case builds on the findings of the latest photographs. The clinical reports and the conclusions relating to the material thus diagnosed, as well as the prophylactic measures taken, will be published shortly by LAVONIUS in »Nordisk Medicin». A closer discussion of same will therefore not come into question in the present connection. Only the following interesting

observations may be touched upon for the sake of comparison with the above-mentioned general clinical data and compilations. Not a single case of tuberculosis was found within the whole range of the asbestosis material. This finding agrees with MEREWETHER's opinion as to the slight importance of the tuberculosis component in cases of asbestosis, which contrasts with the generally recognized tendency of silicosis to predispose to tuberculosis. There was likewise not a single case of carcinoma. Our material does not allow of any more exhaustive conclusions being drawn with regard to the duration of exposure to asbestos dust in relation to the manifestation and progression of asbestosis in different stages. This depends on the fact that in Finland this occupational disease has only during the past three years been made the subject of observations, although the mining of asbestos and the dressing and working up of same has already been carried on here for about 20 years. It is thus conceivable that asbestosis of varying degrees can have been caused during this period, without it now-a-days being possible to judge its progressivity. The only figures available to us are the period of work whilst exposed to asbestos dust in relation to demonstrated stages of asbestosis. The milder stages I and I—II (for closer particulars relating to the roentgenological findings see the following section of this publication) have thus been established as existing in the case of 94 workers (75 %) with an average mean exposure of 3.4 years. The medium stages II and II—III are found in the case of 23 workers (18 %) with an average exposure of 7.9 years and the most advanced stage, III, in the case of 9 workers (7 %) with an average exposure of 11.5 years. For particulars with regard to the kind of work, the massiveness of the dust exposure and closer clinical data in these cases affected by asbestosis the reader is referred to LAVONIUS. As pointed out above, it is only during the past three years that it has been possible to study the progression of asbestosis. During the observation time of 2 years, 27 or 75 % of the 36 cases in the ante-primary stage which were first observed have progressed to stage I (cfr. page 150). Within stage I 4 of the 32 cases (12.5 %) have progressed to the intermediate stage I—II, while the same number have passed to stage II. Within stage II 2 out of 10 (20 %) have advanced to the intermediate stage II—III, whence no progression to stage III has been observed. Before the commencement of the examinations, two known deaths occurred in asbestosis and have been pathologically-anatomically investigated (LAVONIUS and also NORO). In addition, in all probability other deaths have occurred in indirect connection with asbestosis, more especially among the workers in the dressing work in the asbestos mine. However, reliable information is no longer to be had with regard to such cases.

The Roentgen Picture of Lung-Asbestosis and the Interpretation of same

As previously pointed out, the roentgenological changes in the lung picture are the most important diagnostic criteria of asbestosis. The infiltrations described in connection with the pathological anatomy of this infection bring about roentgenologically fairly specific shadows, which will be more particularly discussed below. To this must naturally be added the secondary complications, in so far as they are roentgenologically observable. Like the radiologically delimitable stages in silicosis, also asbestosis can be divided into varyingly severe stages of development. In this respect there are two different methods of classification available, the German one in four stages, given by SAUPE, and the American one in three stages, put forward by SHULL.

Saupe's Method of Division.

The ante-primary stage of asbestosis: still fairly uncharacteristic strengthening of the lung picture, mainly in the middle and basal fields, fine ray shadows and quite slight indications of small nodules in the costophrenic or cardiophrenic angles respectively.

Asbestosis I: extremely fine network in the middle and basal fields of the lung picture, which is already layered with very small soft spots.

Asbestosis II: denser lung picture, more numerous extremely small nodule shadows, beginning decrease in clarity of the middle and basal fields, more especially of the areas close to the heart. Hila broad and dense, in general without lime layering.

Asbestosis III: marked shadowing of the middle and basal fields in contrast to increased ray-permeable emphysematic apic fields. The contours of the heart are difficult to differentiate against the densified lung tissue. Hila broader, but not specially dense.

The border cases, which cannot without further be differentiated in the stages in question are referred to the intermediate stages (I—II and II—III).

Shull's Method of Division.

1. *Incipient asbestosis:* light interstitial fibrosis in both lungs towards the base, the picture appears hazy.

2. *Moderately advanced asbestosis:* more pregnant interstitial fibrosis extended to the periphery of the basal two thirds of the lungs, resembling »a ground glass appearance». Increased bronchovascular marking. Slight thickenings of the pleura and pericardium. The right side of the heart is often dilated, occasionally also slight apical emphysema.

Fig. 5. Asbestosis, stage I. Fine network in the middle and basal fields of the lung picture, already layered with small soft spots.

3. *Severe advanced asbestosis:* strongly marked haziness or shadowing of the basal two thirds of the lungs. Emphysematous configuration of the thorax, with frequently highly developed apical emphysema, marked right side hypertrophy of the heart. Heart contour of »shaggy outline», difficult to differentiate against the parenchyma. Almost always marked thickenings of the pleura and pericardium.

In classifying my own asbestosis material of 126 cases, I have preferred to use SAUPE's division into one ante-primary stage and three manifest stages, together with intermediate stages, in preference to SHULL's method, which in reality implies the leaving out of the ante-primary stage and also the intermediate stages. In practice the present method of division has shown itself to be very usable, both in regard to prophylaxis and to questions of insurance and compensations (see LAVONIUS). As pointed out by SAUPE in his later work of the year 1939, owing to its specific pathological-anatomical structure, a commencing asbestosis brings about an increase of the lung marking of such extremely fine caliber, that it is both technically difficult to reproduce and differential-diagnostically difficult to distinguish from the irritation arising in cases of inflammatory hypertrophy and bronchitis. As such an irritation, however, can with good reason be thought to constitute the base for an asbestosis arising later, it is certainly not prejudicial to the matter to have also such cases brought under special observation and continuous serial control. In conformity with the wishes of the Finnish Insurance Companies both ante-primary stages and manifest cases of asbestosis are to be control-photographed once yearly by means of ro nt-

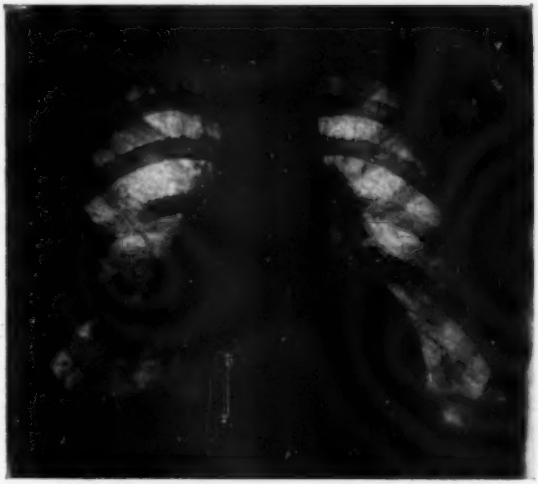

Fig. 6. Asbestosis, stage I—II. More pregnant interstitial fibrosis extended to the periphery of the basal two thirds of the lungs. Increased broncho-vascular marking. Slight thickening of pleura. Beginning enlargement of the heart. Hili broad and dense.

gen. From my observations it appears, however, that the ranging of the ante-primary stage among the asbestosis cases would to some extent be warranted. When first photographed in 1944 36 cases were classified as stage 0—I. At the most recent examination 2 years later 19 of these cases or a good half showed a manifest asbestosis of stages I or I—II. This observation tends to contradict the sceptical opinion against early roentgen diagnosis of asbestosis which is held by *i. a.* PENDERGRASS. In my reports I have, however, for precautional reasons not included the ante-primary stages among the manifest cases of asbestosis. This has been done partly in view of the undeniably great possibilities of faulty diagnosis in the extremely subtile changes of the ante-primary stage, and partly in order to avoid an unwarranted and possibly injurious psychosis as regards industrial disease in the case of the person concerned, should he become aware of such a diagnosis.

In contrast to the very typical different stages of silicosis, the stages of asbestosis cannot be so distinctly delimited, this being due to the much coarser morphological changes in the former disease. Already for this reason the use of the intermediate stages I—II and II—III is warranted. Besides this, the practical advantages of such a division from prophylactic and insurance-technical points of view must be taken into consideration. As duly set forth by Mr. LAVONIUS, the prophylaxis against pneumoconiosis is in Finland more especially directed towards the removal of persons suffering from manifest asbestosis from work exposed to the risks thereof, with special regard to the varying progression of the disease in different age groups. A more detailed classification

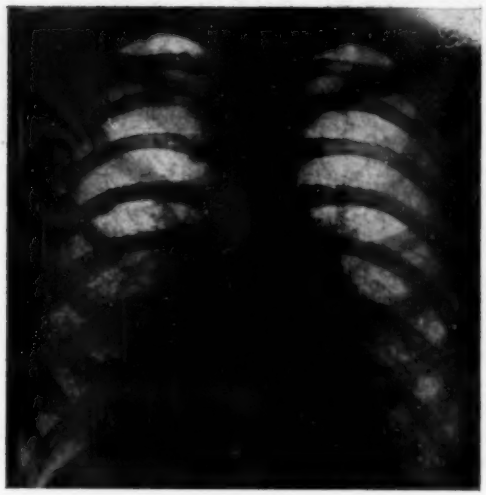

Fig. 7. Asbestosis, stage II. Hypoventilation of the lung fields and denser lung picture everywhere. Beginning emphysema in the right costo-phrenic angle. Hili dense. The vascular trunk shadows have largely lost their identity, probably due to thickening of the pleuropericardium.

in such cases naturally tends to increase the possibilities of accurate protective measures. Even although the differentiation of the various transition stages of asbestosis by means of absolute measurements can vary and meet with difficulties, the tendency of the pathological process can in this way on the whole be more correctly reproduced.

Roentgen investigation of asbestosis ought in my opinion to take place by means of photographs. In these cases fluoroscopy of the lungs cannot be ascribed any greater diagnostic value. Besides the great importance of the roentgenogram as documentary evidence both for the time being and for subsequent comparative studies of the progression of the process (WEGELIUS), only the film permits the demonstration of early, more subtile alterations. Illustrative of this are the following observations made by me: The use of fluoroscopy did not enable any diagnoses of »ante-primary stages» to be made in 36 investigated cases, stages 0—I. Among 64 cases, stages I and I—II, the diagnosis »increased marking in the basal fields» could be given solely on the basis of fluoroscopy in only 16 cases (25 %). In the stages II, II—III and III palpable changes could certainly be observed in all cases where use was made of fluoroscopy, but no closer classification was possible. Naturally, however, as especially pointed out by PENDERGRASS, fluoroscopy has its value for the determination of conditions connected with the mobility of the thoracic organs. In this respect emphysema and adhesions of the pleura come mainly into question.

The asbestosis picture's character of a superimposed fine-meshed net-

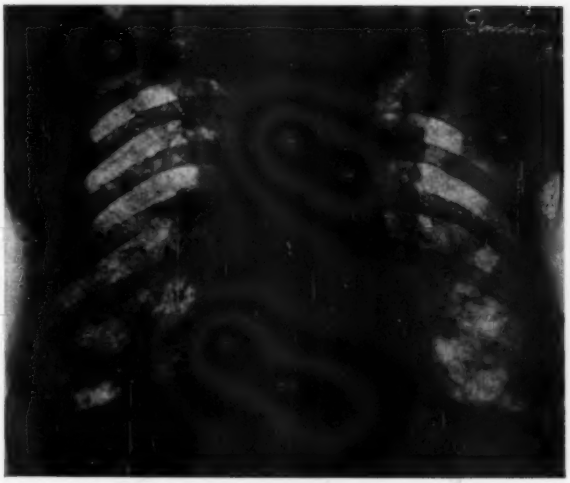

Fig. 8. Asbestosis, stage II–III. Asbestosis markedly advanced. The lesion occupies the lower and middle lung fields. In the upper right field a beginning hyperventilation, emphysema. In the upper left field is heavy fibrosis and probably thickening of the paramediastinal pleura. The cardiac outline is quite indistinct, due to thickening of the pleurapericardium and superimposed shadows in the lung fields. Hili broad and dense.

shadowing calls for the best possible technical conditions to ensure sharpness of reproduction and contrast. On account of the lime-poor nature of the changes, the asbestosis diagnosis demands relatively soft lung pictures. In such case, however, all extra-pulmonal, disturbing shadows, in the first place the mamma shadows, are found to be strengthened in a high degree. SAUPE has specially pointed out how important it is when photographing to eliminate — by elevating or pushing aside both breasts of the subject — their disturbing and misleading effect. As pointed out above, the incipient cases of asbestosis are localized just in the lung bases and are best observed in the costo-phrenic angle itself (see fig. 6), where the disturbing effect of the mamma shadows can be especially serious. Due heed must also be paid to the corresponding effect of the pectoral muscles. In special cases completing pictures in oblique projections can give a clearer view of the diagnostically important parts of the lung base than is obtainable by the standard projection in the frontal plane. Differential-diagnostically stasis in the blood and lymphatic vessels, miliary tuberculosis, general carcinosis, post-inflammatory changes, bronchitis and bronchiolitis come into question. However, in the case of asbestosis, the net-shadowing, which is to a certain extent specific, and the symmetrical predilection for the basal parts, make a distinction from the aforesaid conditions considerably easier than might be thought. As pointed out by SAUPE, the radiological differential diagnosis against true silicosis is in general not difficult, owing to the shadow formations of this affection differing so considerably from those of asbestosis. The unspecific, so-called silicatoses, which are related to silicosis, can, how-

Fig. 9. Asbestosis, stage III. Very strongly marked shadowing of the entire lung fields. Emphysematous configuration of the thorax with highly developed apical emphysema, specially on the left side. Indistinct outline of the cardiac silhouette on the right side, due to thickening of the pleuropericardium.

ever, to a bewildering degree resemble the picture of asbestosis, especially in more advanced stages, where the general fibrotic induration is dominant.

Table I.

	Classification, % of total.	Complications (several complications may occur in one and the same case), % within the stage.			
	Cases	Emphysema	Pleura & Pericardium thicken.	Heart-enlargement	No complications
Mild stage:					
Asbestosis I	79 (63 %)	4 (5 %)	14 (18 %)	5 (6 %)	63 (80 %)
» I—II.....	15 (12 %)	3 (20 %)	6 (40 %)	1 (7 %)	7 (47 %)
Medium stage:					
Asbestosis II	19 (15 %)	11 (58 %)	13 (68 %)	1 (5 %)	3 (16 %)
» II—III.....	4 (3 %)	4 (100 %)	4 (100 %)	2 (50 %)	—
Far advanced stage:					
Asbestosis III.....	9 (7 %)	9 (100 %)	9 (100 %)	4 (44 %)	—
Total	126	31 (25 %)	46 (36 %)	13 (10 %)	73 (58 %)

The classification of my material on the basis of the most recent roentgenogram in every case is shown in Table I, containing also the most important subsidiary findings and complications observed. As appears from the tabular compilation, uncomplicated cases of pure asbestosis are almost without exception to be found only in the milder stages I and I—II. In the moderate stages emphysema and thickenings of the pleura and pericardium are very common, becoming obligatory in stages II—III and III. Enlargement of the heart occurs, however, more

Fig. 10. Asbestosis, stage I. Early manifestations indicated by the beginning obliteration of the costo-phrenic angle. Typical fine network picture in the lowest lateral part of the basal lung field.

seldom than stated in literature; as will be seen, the percentages for same lie below 10 % in the milder and moderate stages and are not higher than 50 % in the most advanced stages.

The fairly high percentage of more advanced asbestosis — as compared with statistics from other countries — probably depends on the fact that the industrial disease in question has so recently as only some few years ago been found to occur here and brought under control. Now that careful supervision is exercized by means of annual roentgen photography, the high figures for more advanced stages will certainly be reduced, more especially in the case of newly engaged workers. This postulates, however, a reliable roentgen diagnosis of the disease asbestosis. For this reason it is necessary to undertake scrupulously exact investigations of this occupational disease, which is practically unknown in Scandinavia. By comparisons between our own published results and those arrived at by means of corresponding investigations in other countries, we can learn to master this serious disease, in which, in the absence of effective therapy, diagnosis and prophylaxis are decisive.

SUMMARY

Asbestosis of the lungs is an industrial disease not often hitherto observed in Scandinavia, only five cases have been published from Norway. In Finland, where a con-

siderable asbestos industry has been established for a couple of decades, asbestosis of the lungs appears to occur to an appreciable extent. The author gives an account of 126 cases of asbestosis of the lungs, 94 or 75 % of these cases being in the mild, 23 or 18 % in the moderate and 9 or 7 % in the advanced stage of asbestosis. The roentgenological characteristics of the changes in the lungs, the differential diagnosis, the classification in different stages and the importance of the time of exposure are discussed in detail. The different stages of asbestosis of the lungs are illustrated by typical pictures.

ZUSAMMENFASSUNG

Die Lungenasbestose ist eine Berufskrankheit, die bis hierher in Skandinavien nicht sehr oft beobachtet ist. Nur 5 Fälle aus Norwegen sind publiziert worden. In Finnland, wo seit ein Paar Jahrzehnten eine beträchtliche Asbestindustrie existiert, scheint die Lungenasbestose eine ziemlich grosse Ausbreitung erhalten zu haben. Der Verfasser beschreibt 126 Fälle von Lungenasbestose, von denen 94 (75 %) leichte, 23 (18 %) mittelschwere und 9 (7 %) schwere Fälle. Die röntgenologischen Kennzeichen der Lungenveränderungen, die Differentialdiagnose, die Klassifikation der verschiedenen Stadien sowie die Bedeutung der Expositionszeit wird näher diskutiert. Die verschiedenen Gräde der Lungenasbestose werden mit typischen Bildern illustriert.

RÉSUMÉ

L'amiantose des poumons est une maladie professionelle qui jusq'au présent n'a pas souvent été observée en Scandinavie. Seuls 5 cas ont été rapportés de Norvège. Dans la Finlande, qui depuis quelques dizaines d'années possède une industrie d'amiante assez considérable, l'amiantose des poumons parait être assez repandue. L'auteur nous explique 126 cas d'amiantose des poumons, dont 94 cas (75 %) bénins, 23 cas (18 %) médiocres et 9 cas (7 %) graves. Les signes radioscopiques des changements des poumons, le diagnostic différentiel, la classification en phases différentes ainsi que l'importance du temps de l'exposition sont discutés de plus près. Les différents degrés de l'amiantose des poumons sont illustrés par des photos caractéristiques.

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FROM THE RADIUM CENTER, COPENHAGEN (CHIEF: JENS NIELSEN, M. D.)

PREOPERATIVE ROENTGEN TREATMENT IN BREAST CANCER[1]

by

Sigvard Kaae

The treatment of operable breast cancer is primarily surgical operation, consisting in removal of the breast with plenty of skin, both pectoral muscles and the axillary adipose tissue with lymph nodes. The radiologic treatment is at most an adjuvant to this, and opinion still differs as to its value (see, for instance, PACK & LIVINGSTON). The radiologic treatment may be given preoperatively or postoperatively, or both pre- and postoperatively, and either with roentgen or with radium. Roentgen treatment is the most usual, and the tendency has been toward preoperative roentgen, if indicated in connexion with postoperative.

In the last few years some hospitals have, however, again abandoned the preopertive roentgen treatment, among them the New York Memorial Hospital, where special interest had been given to that form of treatment in cases of breast cancer.

What results the different therapeutic modifications are capable of producing can only be estimated and an expression for their relative value only found statistically. But statistics often suffer from errors, shortcomings or imperfections which the author or the reader does not always realise, and which may lead him to draw conclusions for which there is no statistical basis. A simple, fundamental condition is that the clinical materials compared with reference to some particular factor, for instance a therapeutic modification, shall be alike as regards all other factors capable of playing a rôle for the basis of comparison (the survival curve, for instance) and only differ as regards the factor which is the object of examination. Thus, if in two different hospitals different treatments have been employed for the same affection, and the results

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obtained in one of them are so much better than those obtained in the other as to be statistically significant, this difference cannot rightly be ascribed either exclusively or partly to the treatment unless there is sufficient evidence to show that the two patient materials have been absolutely alike. When it is a question of comparing the results of the treatment of operable breast cancer by radical surgery only and by radical surgery supplemented with roentgen, this presupposes that the surgical operations have been carried out in exactly the same manner and on patient materials exactly similar, so that the difference lies only in the supplementary roentgen treatment.

At the Radium Center in Copenhagen, preoperative roentgen treatment, partly in connexion with postoperative, has since 1931 been used in all the cases of untreated, operable breast cancer referred to the Center. The surgical operation has in most of them been performed in the surgical service of the Finsen Institute. Operation has been done not only in the surely operable cases and the borderline cases, but also in those which, though at first considered as inoperable, became operable following the roentgen treatment. Reports of the results have already been published by JENS NIELSEN, the last in 1942. In order to arrive at a conclusive estimate of the value of the roentgen treatment given, I have made an analysis of the material from the period 1931—1942, as it stood at the end of 1944 (Table I). It comprises 301 patients with an observation time from 2 to 13 years; for 137 of them 5 years or more. They have all been followed during the entire period of observation, and the diagnosis of cancer has been histologically verified in all the cases.

The cases are divided into two groups — stage I and stage II — according to the result of the histologic examination of the contents of the axilla. Stage I comprises those in which cancer was present only

Table I.

Radical surgery combined with preoperative — in some cases also postoperative — roentgen treatment in breast cancer at the Radium Center in Copenhagen 1931—1942.

Years	Total number	Stage I	Stage II	Alive			Symptom-free		
				Total	Stage I	Stage II	Total	Stage I	Stage II
7	98	51 %	49 %	42 %	54 %	30 %	40 %	54 %	26 %
6	113	49 %	51 %	47 %	60 %	33 %	43 %	55 %	31 %
5	137	50 %	50 %	55 %	69 %	41 %	49 %	65 %	33 %
4	169	48 %	52 %	60 %	73 %	47 %	54 %	68 %	40 %
3	250	50 %	50 %	72 %	86 %	58 %	60 %	77 %	42 %
2	301	49 %	51 %	80 %	90 %	71 %	70 %	86 %	53 %
1	301	49 %	51 %	92 %	97 %	87 %	82 %	92 %	73 %

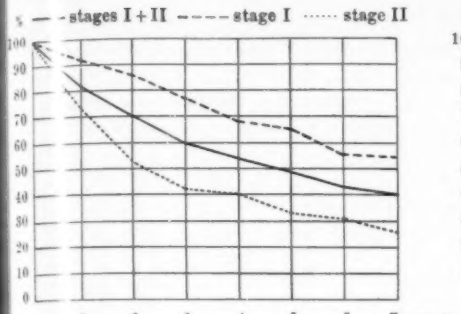

Fig. 1.

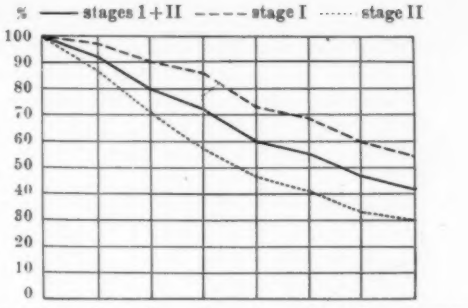

Fig. 2.

Fig. 1. Curves showing the symptom-free survival per cent (crude cure rate) in breast cancer at the Radium Center, Copenhagen, for radical surgery combined with pre-operative roentgen treatment.

Fig. 2. Curves showing total survival per cent in breast cancer at the Radium Center, Copenhagen, for radical surgery combined with preoperative roentgen treatment.

in the mamma, stage II those in which also the axillary lymph nodes were involved. It is very important to hold to this form of classification, which is undoubtedly the best. The classification based wholly or partly on enlarged axillary nodes found clinically or by operation cannot be compared with it, because the clinical estimation is very open to error. Thus, HARRINGTON (1935) shows in an analysis of a large material that in 32 percent of the cases in which enlargement of the nodes had been found clinically no cancer was found histologically, the enlarged nodes being only inflamed; and in 29 per cent of the cases in which nodal enlargement was not found clinically the histologic examination showed axillary metastasis.

Fig. 1 shows the symptom-free survival rate — that is the crude cure rate, no correction having been made for patients who died owing to complications from operation or free from symptoms. The curves are plotted for the first seven years following treatment. There are 98 cases with an observation time of at least that length. There are curves for both stages together and for each stage separately. The five year symptom-free survival rate is for both stages together 49 per cent, for stage I 65 per cent, for stage II 33 per cent.

Fig. 2 shows the total survival rate (*i. e.* all survivals, whether symptom free or not). The five year rate is here for both stages together 55 per cent, for stage I 69 per cent, for stage II 41 per cent.

The ideal material for comparison with the preoperatively roentgen-treated cases would be a group of patients operated on in the same hospi-

Table II.

Radical surgery combined with postoperative roentgen treatment in breast cancer at the Radium Center in Copenhagen 1931—1942.

Years	Total number	Stage I	Stage II	Stage ?	Alive			Symptom-free		
					Total	Stage I	Stage II	Total	Stage I	Stage II
7	126	47 %	48 %	5 %	33 %	54 %	15 %	30 %	47 %	15 %
6	158	46 %	50 %	4 %	37 %	61 %	16 %	35 %	57 %	16 %
5	184	44 %	52 %	4 %	42 %	65 %	25 %	35 %	59 %	17 %
4	207	43 %	53 %	3 %	46 %	68 %	31 %	39 %	62 %	22 %
3	228	44 %	53 %	3 %	57 %	73 %	46 %	44 %	67 %	26 %
2	249	43 %	54 %	3 %	71 %	84 %	62 %	52 %	75 %	36 %
1	249	43 %	54 %	3 %	88 %	94 %	85 %	70 %	88 %	56 %

tal during the same period, but without roentgen treatment. At the Radium Center we have no such group, but a group who had been given only postoperative roentgen in rather small doses (as a rule in two series, one a few weeks after operation, the other two—three months later; in each series 600 to 900 r over each of two large tangential fields on the anterior and lateral surfaces of the thorax and 300 r over a supplementary field in the middle; in recent years, besides, about 1,000 r up in the axilla). These patients had been operated on in various other hospitals, for the most part in the provinces; but in order not to get a poorly selected material I have for the purposes of my analysis included only cases from those which send practically all their breast cancer cases, after operation, to the Radium Center for postoperative treatment. The cases are all from the same period as the preoperatively roentgen-treated. The total number (Table II) is 249; 184 of them have an observation time of five years or over. The diagnosis has been histologically verified in them all, and the patients have been followed during the entire period of observation. They have, like the others, been divided into two groups according to the result of the examination of the axillary contents. In a few per cent there has been no histologic examination of the axillary nodes, — thus in 4 per cent of the five year survivals. These could therefore not be included when it came to calculating the survival rates for stage I and stage II separately. The symptom-free survival rate is for both stages together 35 per cent, for stage I 59 per cent, for stage II 17 per cent; the total survival rate for both stages 42 per cent, for stage I 65 per cent, for stage II 25 per cent.

Figs. 3, 4 and 5 show the curves for survival respectively of the preoperatively and the postoperatively roentgen-treated cases. It will be seen that the results are best for the former, most markedly so for stage

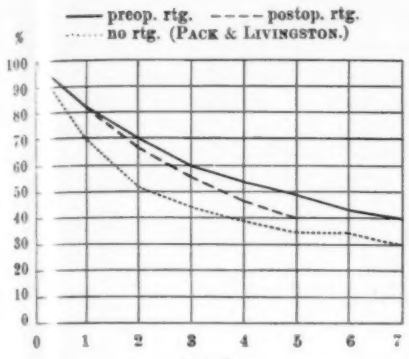

Fig. 3.

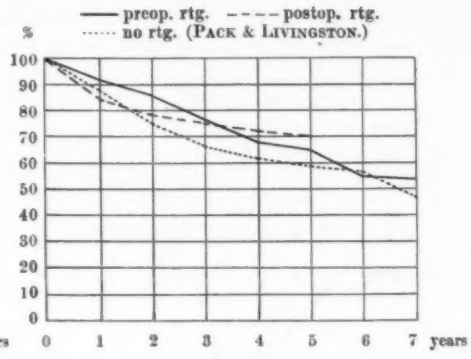

Fig. 4.

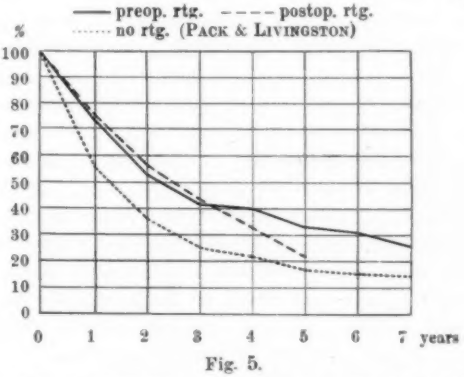

Fig. 5.

Fig. 3. Curves showing symptom-free survivals per cent for histologic stages I + II with radical surgery only (PACK & LIVINGSTON), and combined with pre- or postoperative roentgen treatment (Radium Center, Copenhagen).

Fig. 4. Curves showing symptom-free survival per cent for histologic stage I with radical surgery only (PACK & LIVINGSTON), and with respectively pre- and postoperative roentgen treatment (Radium Center, Copenhagen).

Fig. 5. Curves showing symptom-free survival per cent for histologic stage II with radical surgery only (PACK & LIVINGSTON), and with respectively pre- and postoperative roentgen treatment (Radium Center, Copenhagen).

II, where 33 per cent are alive, symptom-free, after five years, as against 17 per cent of those who got only postoperative roentgen. Among the latter there are no deaths consequent on the operation, because all these patients had been operated on elsewhere. After correction for such deaths among the preoperatively treated, the five year symptom-free survival rate is 34 per cent. The statistical difference for stage II, for five year symptom-free survival, is 1.8 times the standard error. It is,

thus, not statistically significant, but nevertheless rather probable. Since the patient material in the two groups seems to be alike, the better results in the preoperatively treated cases, especially in stage II, must be due to the treatment — either the surgical or the roentgenologic. The surgical operation has in principle been the same in both groups, but it may, of course, have been performed more or less radically. By not including cases from those provincial hospitals which have only sent few patients to the Radium Center for postoperative roentgen treatment, I have probably avoided those least skillfylly operated on, and have thus made it more likely, though not sure, that the difference is due, — partly, at least — to the roentgenologic treatment.

To get another basis for comparison, we may take statistics from other hospitals where radical surgery has been employed without either pre- or postoperative roentgen treatment, and where the classification of the cases has been done after histologic examination of the axillary contents. Curves showing the symptom-free survival rate for the first five years following operation have been published in 1940, by PACK & LIVINGSTON, on the basis of the best U. S. A. statistics of cases treated by surgery only. On Figs. 3, 4 and 5 I have traced in these curves for comparison with those for preoperatively roentgen-treated from the Radium Center. For both stages together (Fig. 3) our results are a little better than the American. Thus, we have a five year symptom-free survival rate of 49 per cent, as against PACK & LIVINGSTON's 40; to which figure we in our material do not get down until seven years after treatment. Our results for stage I (Fig. 4) are for the first three years a little better than the American, after that somewhat poorer; thus, for five year survival: we 65 per cent, PACK & LIVINGSTON 70 per cent. The curves for stage II (Fig. 5) follow more or less the same course for the first three years, then our results get distinctly better than the American; for five years survival: we 33 per cent, they 22, to which figure we do not get down until a little less than eight years after treatment.

The results obtained at the Radium Center with preoperative roentgen treatment are thus slightly poorer for stage I, notably better for stage II, and somewhat better for both stages together, than those shown by the best American statistics for cases treated by surgery only. It is possible that the slightly poorer results for stage I may be due to the inclusion in that group of some cases that should rightly have been listed as stage II. The preoperative roentgen treatment may perhaps cause some lesser metastases to disappear entirely, or to become so small that they are more easily overlooked at the histologic examination. The inclusion of only a few stage II cases in the stage I group will make the results for the latter poorer; at the same time it will take away from the stage II group some cases with presumably slight axillary

Table III.

Five year survival rates in breast cancer, from various statistics, after surgical treatment with and without supplementary roentgen treatment.

Histol. stage	Harrington 1934 without roentgen	Harrington 1934 with suppl. roentgen	Hansson 1940 pre- and postop. roentgen	Radium Center, Copenhagen preop. roentgen	Radium Center, Copenhagen postop. roentgen
I	69.8 %	72.8 %	74.3 %	69 %	65 %
II	24.3 %	28.8 %	23.2 %	41 %	25 %
I + II	44.8 %	41.1 %	44.1 %	55 %	42 %

metastases — that is some of those with the most favorable prognosis within the group; and consequently also the results for this group will be found poorer than they would have been if all the cases had been classed correctly.

In Table III are compared the five year results from various statistics. HARRINGTON has the largest material in the world, of breast cancer cases treated by surgical operation. It now comprises 6,500 cases with an observation time of five years and over. In 1935, he reported the results obtained respectively with surgery alone and with surgery either followed or preceded by roentgen therapy. The figures will be seen from the Table. He found only small difference in the percentage whether treatment was by surgery only or by surgery and roentgen. That the results for both stages together are poorer in cases in which roentgenologic therapy was added to the surgical treatment is because the proportion of stage II cases is larger in this group. By grading the cases according to Broders' method he found, however, some improvement in the results obtained by supplementary roentgen treatment in the prognostically poorest grades III and IV. If we compare the results in those of HARRINGTON's cases in which the treatment was by surgery only, with those obtained at the Radium Center when preoperative roentgen treatment had been given, the latter are found to be better for stage II and for both stages together, while they are alike for stage I. On statistical evaluation of the difference, for stage II, between HARRINGTON's only surgically treated cases and the Radium Center's preoperatively roentgen-treated, the difference is found to be 2.7 times the standard error, and should thus be statistically significant. HANSSON has in 1940 reported the five year results for pre- and postoperatively roentgen-treated cases from the Radiumhemmet in Stockholm. Also a comparison with these shows better results for the Radium Center in Copenhagen, both for stage II and for both stages together, but slightly poorer for stage I.

Table IV.

Five year symptom-free survival rates in breast cancer, from various statistics, after surgical treatment with and without supplementary roentgen treatment.

Histol. stage	Pack & Livingstone 1940 without roentgen	Ahlbom 1941 pre- and postop. roentgen	Radium Center, Copenhagen preop. roentgen	Radium Center, Copenhagen postop. roentgen
I	70 %	71 %	65 %	59 %
II	22 %	24 %	33 %	17 %
I + II	40 %	41 %	49 %	35 %

In Table IV are compared the five year results, with freedom from symptoms, obtained respectively by PACK & LIVINGSTON with surgery alone, by AHLBOM (1941) at the Radiumhemmet in Stockholm with pre- and postoperative roentgen, and our material from the Radium Center. The American and Swedish results are practically alike, those of the Radium Center slightly poorer for stage I, distinctly better for stage II and for both stages together, than any of the others. The conclusion from this must be that the roentgenologic treatment given at the Radium Center in the preoperatively treated cases seems to have improved the results in stage II, and thereby the results for both stages together.

It is curious that the results with pre- and postoperative roentgen treatment of histologic stage II from the Radiumhemmet in Stockholm are not as good as those from the Radium Center in Copenhagen, since the roentgen doses given in Stockholm were of about the same order of magnitude as those employed in Copenhagen before June, 1938 (see below). Perhaps it may to some extent be due, though, to the fact that the technic of irradiation employed was somewhat different in the two places.

The preoperative roentgen therapy employed has varied somewhat. Before June 1st, 1938, 1,000 r (200 r $\times$ 5) were given over each of two tangential fields on the mamma and, as a rule, also over a field up in the axilla. After that time, irradiation has been applied also to a field over the supra-infraclavicular region, directed against the axilla, and larger doses have been given: about 1,800 r (150 $\times$ 12) to the axilllary field and about 2,100 r (150 $\times$ 14) to the others, two treatments being given daily. Factors operated with: 180 kv.; filter, to the supra-infraclavicular field 3 mm. Al at distance 30 cm., to the others 0.5 mm. Cu at distance 40 cm. During a short period, Thoraeus filter was used instead of Cu. Before June 1st, 1938, also a single series of postoperative roentgen was usually given, over two large tangential fields, 800 to 900 r. on each,

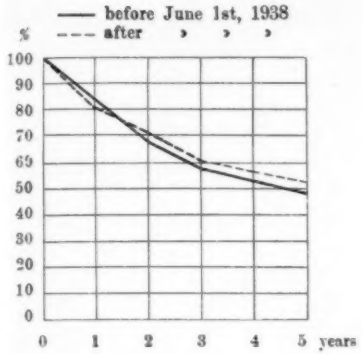

Fig. 6.

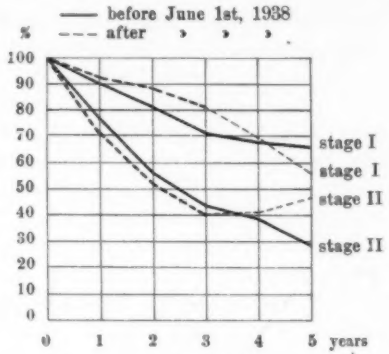

Fig. 7.

Fig. 6. Curves showing the symptom-free survival per cent for histologic stages I + II with moderate pre- and lesser postoperative roentgen treatment (before June 1st, 1938) and with strong preoperative roentgen treatment only (after that date).

Fig. 7. Curves showing the symptom-free survivals per cent for histologic stages I and II separately with moderate pre- and lesser postoperative roentgen treatment (before June 1st, 1938) and with strong preoperative roentgen treatment only (after that date).

and over a supplementary field in the middle, with 250 to 300 r. After June, 1938, there has been no postoperative roentgen treatment.

With a view to seeing if there were any difference between the results obtained with the two different forms of roentgen treatment, the material has been divided into two groups, one comprising the patients treated before June 1938, when less intense preoperative roentgen treatment was given, but in addition a moderate postoperative series; the other comprising the patients treated after that time, with intenser preoperative roentgen alone. The first of these groups comprises 104 cases, all observed for over five years. The second comprises 197 cases, 146 of which have been followed for at least three years, 65 for at least four, and only 33 for five years and over. The four and five year results in this last group are therefore uncertain, especially when we divide the group into two stages. Fig. 6 shows the results for both stages together; they are a little better for those who got preoperative roentgen only, than for the others, but the difference is small. Stage I (Fig. 7) shows better four year, but poorer five year results for preoperative roentgen treatment alone, than the combination of pre- and postoperative treatment. Here, the number of patients is so small, however, that judgment is very uncertain; therefore the curve has also been traced more thinly. Stage II (Fig. 7) shows slightly poorer three year, slightly better five year results, for preoperative

treatment alone, than for the combined pre- and postoperative treatment; but also here it is difficult to form any reliable judgment.

On the whole it thus seems that the intenser preoperative treatment alone does not give better results than a more moderate one combined with a small series of postoperative roentgen. The complications in connexion with the wound healing seem to be greater in the former group; the percentage of deaths due to complications from the operation is higher there: 7.1 as against 1.0 in the other. Perhaps this explains why the results obtained with the intenser preoperative roentgen treatment are not better. The operation mortality for stage II with this form of roentgen treatment is 12.6 per cent (for stage I 3.9 per cent). If we make correction for the deaths in connexion with the operation, the result for stage II becomes just as good for preoperative treatment alone as for preoperative combined with postoperative, but not better than the latter. The fact that the results of the intense preoperative roentgen treatment are not better than those obtained by a moderate preoperative in connexion with small series of postoperative rather seems, however, to speak against the supposition that the preoperative treatment should have improved the results. To this it must be added, though, that the group in which intense preoperative treatment was given contained a larger proportion of cases which primarily had been considered as inoperable owing to carcinomatous lymphangitis or cutaneous metastases in the skin of the breast, or owing to hard supraclavicular glands which raised suspicion of cancer, but which after the intense roentgen treatment were judged to be operable and were subjected to radical operation.

The one death, among the cases prior to June 1938, due to complication in connexion with the operation, was due to embolus of the pulmonary artery. After that date, 5 were due to the same cause, 1 to myocardiac degeneration, arterial hypertension and pneumonia, 6 to postoperative sepsis, 1 to paralytic ileus, 1 to empyema of the gall bladder, peritonitis and bronchopneumonia. In order to find out if this high operation mortality among the patients who had been given the intenser preoperative roentgen treatment is really due to the latter, or is at least partly a matter of chance, I have reckoned up the operation mortality for the two following years, 1943 and 1944, when the same intense preoperative treatment was given, and find that for the 156 cases thus treated it was for both stages together 3.2 per cent, for stage I 1.1 per cent, for stage II 5.5 per cent. This corresponds to the figures stated by most other authors, and the high operation mortality among the patients of the earlier group is thus, at any rate partly, fortuitous.

We have followed the rule, as far as possible, to have the surgical operation performed about four weeks after the termination of the roentgen treatment, but in many cases a longer time has for various reasons

elapsed. In the material are only included those cases in which the interval between the two was not longer than ninety days. In order to see if this time interval had any influence on the result, I have divided the cases into three fairly equal groups, in which the intervals were respectively less than 35, 36—50 and 51—90 days. In the first of these, the result is a little better than for the whole material; thus for both stages together symptom-free five year survival 55 per cent, as against 47 per cent for the latter. In the second group the result was considerably poorer, with only 39 per cent; in the third almost as good as in the first, with 52 per cent of symptom-free five year survivals for both stages together. I cannot find anything to account for this difference, and the result of the examination thus does not tell us anything positive about the possible influence of the length of the interval. It is the general opinion, though, that the operation should be performed as soon as the cutaneous reaction to the irradiation has entirely subsided, three—four weeks after the end of the roentgen treatment.

It is of great interest to consider the relation between the frequency of local recurrence and distant metastases. When such metastases occur without local recurrence it is fairly safe to assume that either they have been present, without yet giving symptoms, already at the time of the operation, or else they have occurred in direct consequence of the latter. In cancer patients, there is supposed to be a regular circulation of cancer cells in the blood stream, which however, according to ENGELBRETH-HOLM among others, does not necessarily give rise to metastases. But at the operation considerable quantities of such cells may easily pass out into the circulating blood and increase the chance of their developing. Of course, it cannot be expected that the preoperative roentgen treatment will have any influence on the latent, distant metastases already present, but it is possible to think that it may injure the cancer cells in the irradiated area in such a manner that those cells that pass into the blood stream in the course of the operation will more rarely give rise to metastases. The preoperative roentgen treatment is, however, believed to have its principal effect by diminishing the risk of local recurrence by killing the cancer cells in the peripheral part of the area involved by the operation, and by causing both the primary tumor and the axillary metastases to shrink, and thereby making it easier to get all of the cancerous tissue removed.

Table V shows the frequency, five years after treatment, of local recurrences (*i. e.* of recurrence as well in the thoracic cicatrix and its surroundings as in the axilla), of distant metastases concomitant with local recurrence, and of distant metastases without simultaneous local recurrence. The frequency of distant metastases concomitant with local recurrence is practically the same as that of local recurrences on the

Table V.

Frequency, five years after treatment, of local recurrence and of metastases, compared with five year results for symptom-free survival.

		local recurrence[1]	metastases		Five year symptom-free survival
			with local recurrence	without local recurrence	
Radium Center, Copenhagen	preop. roentgen	8 %	7 %	36 %	49 %
	postop. roentgen	24 %	24 %	36 %	35 %
Westermark	preop. roentgen	18 %		33 %	50 %
	postop. roentgen	32 %		27 %	37 %

[1] With or without simultaneous metastases.

whole, because metastasising almost invariably appears in the cases where the disease recurs locally. Among the preoperatively roentgen-treated cases at the Radium Center in Copenhagen, there was local recurrence in 8 per cent only, among the postoperatively roentgen-treated in 24 per cent. The difference in five year symptom-free survivals is 15 per cent, and thus very nearly the same as the difference in frequency of local recurrence. This difference may, of course, equally as well be due to the operation as to the form of roentgen treatment given. A report by WESTERMARK, from 1930, on the frequency of local recurrences and metastases respectively among the preoperatively and the postoperatively roentgen-treated cases at the Radiumhemmet in Stockholm, shows similar results. The frequency of distant metastases without local recurrence is even a little greater among the preoperatively treated. The difference in the frequency of local recurrences in the pre- and postoperative groups is 14 per cent, corresponding to a difference in symptom-free survival rate of 13 per cent. The frequency of local recurrence five years after operation is usually stated to be about 20 per cent (HAAGENSEN & STOUT, WHITE); 8 per cent for the preoperatively treated is thus a very low figure, which strongly indicates that the roentgen treatment, so far as this group is concerned, has reduced the frequency of local recurrences and thus increased the percentage of symptomfree survivals.

Table VI shows the frequency of local recurrence respectively in the cicatrix and the axilla, among the preoperatively and the postoperatively treated cases at the Radium Center. That of recurrence in the cicatrix is among the former 8 per cent for both stages together, almost the same in the two; in the axilla, in both stages, 3 per cent. Among the postoperatively treated, there is local recurrence in the cicatrix in 23 per cent, more frequently in stage II than in stage I; in the axilla in 10 per cent,

Table VI.

Frequency of local recurrence in the cicatrix, of local recurrence in the axilla and of metastases in the ipsilateral supraclavicular region.

Radium Center, Copenhagen	Recurrence in cicatrix[1]	Recurrence in axilla[2]	Metastasis in supraclav. region	
			with local recurrence	without local recurrence
preop. stages I + II	8%	3%	4%	4%
preop. stage I	7%	3%	3%	0%
preop. stage II	9%	3%	4%	9%
postop. stages I + II	23%	10%	14%	6%
postop. stage I	11%	5%	6%	2%
postop. stage II	32%	15%	21%	9%

[1] With or without simultaneous recurrence in the axilla.
[2] With or without simultaneous recurrence in the cicatrix.

likewise most frequently in stage II. The table further shows the frequency of lymph node metastases in the ipsilateral supraclavicular region, the first station for metastasis after the axilla, both the cases in which there at the same time was local recurrence and those in which there was no such. Among the preoperatively treated there were in both cases 4 per cent, about equally frequent in the two stages when there was local recurrence; in the absence of local recurrence the frequency of ipsilateral supraclavicular metastases was much greater in stage II. Here, axillary metastasis, and perhaps also incipient supraclavicular metastasis was present already at the time of the operation. Among the postoperatively roentgen-treated, the conditions are similar, only with a much greater frequency of supraclavicular metastases concomitant with local recurrence, corresponding to the greater frequency of the latter.

There is thus in the preoperatively roentgen-treated cases a considerable diminution of the frequency of local recurrence in the cicatrix and the axilla, and of ipsilateral supraclavicular metastases, in the presence of simultaneous local recurrence. The preoperative irradiation should therefore be directed against all these three regions: the breast, the axilla and the supraclavicular.

Also a study of the effect of the roentgen therapy on the different histologic types (best, probably, according to Broders' classification) may be of great value for the estimation of the treatment given. As already mentioned, HARRINGTON has shown that supplementary roentgen treatment may improve the results of surgery in the prognostically poorest grades III and IV. If preoperative irradiation is used, the grading presupposes biopsy, however, before the roentgen treatment, and this was

not used systematically in this connexion at the Radium Center until 1939, when it was introduced in the form of trephine biopsy. Consequently, we have as yet only few five year results. I shall therefore not here go farther into this question.

From all that has been shown in the foregoing it seems that preoperative roentgen treatment, if indicated in connexion with postoperative, may improve the results of surgery in breast cancer. It does not seem that anything is gained by increasing the doses on the individual fields to about 2,000 r, but that a lesser dose, for instance of 1,000 to 1,500 r on each field, will suffice. (This, however, rather seems to speak against any value of the preoperative treatment.) Probably it would then be best to follow with a postoperative series, perhaps of as large doses as the skin will tolerate. Perhaps, also, the intensity of the whole roentgen treatment may be made dependent on a histologic gradation (according to Broders' method, for instance).

Main Results

The author has undertaken his study with the object of examining if the preoperative roentgen therapy used since 1931 at the Radium Center in Copenhagen in cases of breast cancer has improved the results of the surgical operation. For comparison, he has a material of cases from the same period, in which only a lesser, postoperative treatment was given. The analysis shows that the results are considerably better in the preoperatively treated cases. In nearly all these, the surgical operation was, however, performed in the same place (the surgical service of the Finsen Institute), whereas the patients in the cases which were given postoperative roentgen treatment had been operated on, and possibly less radically, in various other hospitals, most of them in the provinces; which makes it impossible to conclude that the difference is due to the roentgen treatment given. He then compares the results in the preoperatively treated cases from the Radium Center with PACK & LIVINGSTON's results for symptom-free survivals from the best U. S. A. statistics of cases treated by surgely only, and with HARRINGTON's results for five year survival, likewise in cases treated by surgery only, and finds that those obtained at the Radium Center by the combination of preoperative radiation and surgery are distinctly better than any of them for both the histologically verified stages I and II together, as well as for stage II, but a little poorer for stage I.

The roentgen treatment has varied somewhat. Prior to June 1st, 1938, a moderate preoperative treatment was given, supplemented by a lesser postoperative; after that time only a strong preoperative. The results seem to be about the same. An examination of the frequency

or local recurrence in the cicatrix and the axilla respectively in the preand the postoperatively treated cases five years after treatment, and comparison with the number of five year symptom-free survivals, shows that the lesser frequency of local recurrence in the preoperatively treated cases corresponds exactly to the better five year results, while the frequency of distant metastases without local recurrence is the same in the two groups. The incidence of local recurrence respectively in the cicatrix and in the axilla, and the frequency of metastases in the ipsilateral supraclavicular region, are examined with a view to finding where the irradiation should best be applied. It seems that it should be directed to fields over each of these sites. Finally, the author mentions the possible value of histologic gradation, for instance according to Broders' method.

SUMMARY

The author has analysed the results obtained at the Radium Center in Copenhagen in breast cancer cases treated by radical surgery either followed or preceded by roentgen therapy, and has compared them with the results obtained in various other hospitals. While he finds nothing in the literature which with certainty proves that preoperative roentgen treatment improves the results of the surgical operation, he thinks that his own material — which is not very large, however — seems to indicate that such may nevertheless be the case. It does not appear that anything is gained by greatly intensifying the preoperative roentgen dose. The frequency of distant metastases without simultaneous local recurrence was the same in the preoperatively and the postoperatively roentgen-treated group, whereas the frequency of local recurrence was so much greater in the postoperatively treated that it may perhaps explain the better results in the preoperatively treated.

ZUSAMMENFASSUNG

Verf. hat die Ergebnisse analysiert, die in der Radiumzentrale in Kopenhagen bei Brustkrebs erzielt wurden, der mit Radikaloperation und voraufgehender oder nachfolgender Röntgenbestrahlung behandelt worden war, und hat diese Ergebnisse mit den in verschiedenen anderen Krankenhäusern erzielten Resultaten verglichen. Während er im Schrifttum keinen sicheren Beweis dafür finden kann, dass präoperative Röntgenbehandlung die Ergebnisse des chirurgischen Eingriffs verbessert, meint er, dass sein eigenes — freilich nicht besonders grosses — Material anzudeuten scheint, dass dies immerhin der Fall sein kann. Es scheint nicht, dass man durch bedeutend intensivere präoperative Röntgendosis irgend etwas gewinnt. Die Häufigkeit von Fernmetastasen ohne gleichzeitigen lokalen Rückfall war in der präoperativ und in der postoperativ röntgenbehandelten Gruppe die gleiche, während die Häufigkeit lokaler Rezidive in der postoperativ behandelten so viel grösser war, dass dies die besseren Ergebnisse der präoperativ behandelten vielleicht erklären kann.

RÉSUMÉ

L'auteur a analysé les résultats obtenus au Centre du Radium de Copenhague dans les cancers du sein soumis à l'opération radicale suivie, ou précédée, de radiothérapie,

et les a comparés à ceux de divers autres hôpitaux. Bien que dans la littérature il ne trouve rien qui prouve avec certitude que le traitement préopératoire par les Rayons Roentgen améliore le pronostic de l'intervention chirurgicale il pense cependant que son propre matériel — à vrai dire pas très considérable — semble indiquer que cela puisse, pourtant, être le cas. Il ne paraît pas qu'on gagne quoi qui ce soit en intensifiant grandement la dose préopératoire des Rayons Roentgen. La fréquence des métastases à distance sans récidive locale simultanée fut la même dans les groupes traités par les Rayons Roentgen avant ou après l'intervention chirurgicale, tandis que celle des récidives in situ fut tellement plus grande chez les malades soumises à la radiothérapie postopératoire que cela expliquerait peut-être les meilleurs résultats obtenus dans les cas irradiés préopératoirement.

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FURTHER DEVELOPMENT OF THE THEORY OF BIOLOGICAL REACTIONS CAUSED BY ROENTGEN RAYS[1]

by

J. Th. van der Werff, M. D. Sc. D.

1. Since DESSAUER, BLAU and ALTENBURGER (1923) for the first time introduced the mathematical methods into the problem of biological action of Roentgen-rays, many other attempts in this direction have been made. Partly the theorists built on DESSAUER's idea and so the different hit-theories originated. It then proved necessary to take into consideration, that a biological object may recover more or less from the injury by irradiation (RAJEWSKI & DÄNZER 1934, LEA 1938).

However, the problem of the recovering-potency has also been treated mathematically independently of the hit-theories by HOFFMANN & REINHARD (1934), by QUIMBY & MAC COMB (1936), by SIEVERT (1941) and by the present author (1942). It was SIEVERT who, for the first time, introduced the idea, that there must be a certain phase-difference between the injury and the recovery. When the author criticized SIEVERT's equations and, preserving the basic idea, replaced the theory by a new one, he was convinced that this would only be a new step and that further criticism probably would occasion further development. This has happened indeed and in this paper I may communicate some of the results.

Firstly the principles may shortly be repeated.

It was premised that in biological objects there is an ever-lasting building-up and breaking-down, in other words, that one has always to take into consideration the already existing metabolism. From the investigations of the last years it has been clear, that even the elementary albumen-molecules are in a certain sense living objects and are continuously being built up and broken down. *I may even maintain that each theory on a biological problem, that does not take the existing metabolism into*

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account, has been condemned a priori already, because it neglects the most essential principle of Life.

If the radiosensitive substance X is in a steady state before the irradiation begins, then there is always a dynamical equilibrium between the number of elements that is broken down in a time-unit and that which is built up in the same time. By irradiation with Roentgen or γ-rays the number of elements which is broken down in a time-unit increases.

It was supposed that, as a consequence of this process, the number of elements, built up in a time-unit, would increase as well, in other words that the increased breaking-down would stimulate an increasing building-up. The last process, however, would follow the first one after a certain latency-time τ. The following hypothetical equation resulted

$$\frac{d\xi(t)}{dt} = -I(t)\,\xi(t) + L(t-\tau)\,\varrho(t) \quad \ldots\ldots\ldots \quad (1)$$

In this equation $\xi(t)$ is the number of elements of X at the time t, $\varrho(t)$ that of the reserves or the new matter out of which X is built up. $I(t)$ and $L(t-\tau)$ are called the dissimilation- and assimilation-coefficients.[1]

In the steady state $\varrho(t) = \varrho_0$, $I(t) = I_0$ and $L(t) = L(t-\tau) = L_0$ are all constants and therefore necessarily also $\xi(t) = \xi_0$, constant.

During the irradiation the dissimilation-coefficient is increased from I_0 to $I_0 + I$, where in a first approximation I is supposed to be proportional to the intensity of the irradiation. After τ sec L_0 also increases to $L_0 + L$. Finally it was assumed that the assimilation-coefficient, apart from the latency-time was always proportional to the dissimilation-coefficient.

In case $\varrho(t)$ remains always ϱ_0 (so the reserves are supposed to be not-radiosensitive and present in such a quantity, that their number practically does not change during the irradiation), it was possible to reduce equation 1) to

$$\frac{d\xi(t)}{dt} = -I(t)\,\xi(t) + I(t-\tau)\,\xi_0$$

or

$$\frac{dx(t)}{dt} = -I(t)\,x(t) + I(t-\tau) \quad \ldots\ldots\ldots \quad (2)$$

In this equation $x(t) = \frac{\xi(t)}{\xi_0}$ is the relative concentration with respect to the steady state.

[1] In the previous paper, written in German, I called the coefficients »Verbrauchskoeffizient« and »Erhohlungskoeffizient«. I think it better, however, to replace these terms by dissimilation- and assimilation-coefficient.

If the elements of X serve to build up another substance Y and if this substance itself is not radiosensitive, then

$$\frac{dy(t)}{dt} = -J_0 y(t) + J_0 x(t-\tau')$$

etc.

With the aid of these equations it was possible to give an explanation of the many undulating phenomena, which occur so often in biological objects after roentgen irradiation and which have a diphasic course in many cases. In particular there was a fair concordance with the experiments of A. FORSSBERG on the fungus-cell Phycomyces Blakesleeanus, as far as these had been published at that time.

2. In 1943 FORSSBERG published a complete description of his experiments. In his monograph he tested the results against SIEVERT's theory. As for the author's theory he judged it a supposition difficult to prove that the assimilation-coefficient should always be proportional to the dissimilation-coefficient. I must admit indeed, that this is a weak point in the theory. A further examination even shows that this supposition is not only undesirable but even superfluous and that the giving-up of the hypothesis leads to important consequences for our insight into the action of Roentgen-rays and to a complete agreement with all FORSSBERG's experimental findings.

Firstly we may ask what physical events may underlie the changes of the dissimilation- and assimilation-coefficients. However intricate the events of metabolism may be, one thing is sure: different ions play an important part. I may recall the words of SZENT-GYÖRGYI: »I was always led in research by my conviction that the primitive basic functions of living matter are brought about by ions, ions being the only powerful tools which life found in the sea-water where it originated.»

One may suppose that in the steady state I_0 and L_0 are nothing but measures for the concentration of certain groups of ions, which, by their activating work, regulate the rate of breaking-down or building-up.

If a biological object is irradiated by X- or γ-rays, then directly or indirectly the concentrations of these ions may be enlarged and thus the dissimilation-coefficient and the assimilation-coefficient may also be enlarged independently of each other. So it is not necessary at all that the accelerated assimilation is a delayed reaction to the dissimilation. It remains possible that some demolition-products play a stimulating part, but next to it the irradiation itself may produce ions which enhance the assimilation-velocity. It is in fact not necessary that the absorbed energy is only used for destruction.

It will however be clear that in general the destruction will be easier than the more intricate synthesis and so each change in the assimilation-

coefficient will develop more slowly than a change in the dissimilatio n-coefficient. If we now also accept a relaxation-time for the change in the dissimilation-coefficient (which may be very small) and further assume that the enlargement of both coefficients is, in a first approximation, proportional to the intensity of the radiation, then the new »equation of metabolism» obtains

$$\frac{d\xi(t)}{dt} = -\{I_0 + c_1 i_{t-\tau_1}\}\,\xi(t) + \{L_0 + c_2 i_{t-\tau_2}\}\,\varrho(t) \quad . \quad . \quad . \quad . \quad (3)$$

where c_1 and c_2 are constants, depending on the object. If the properties of the object are such that the reserves are not radiosensitive and do not alter during the irradiation, so that always $\varrho(t) = \varrho_0$, this equation may be reduced to

$$\frac{dx(t)}{dt} = -I_0\{1 + k_1 i_{t-\tau_1}\}\,x(t) + I_0\{1 + k_2 i_{t-\tau_2}\} \quad . \quad . \quad . \quad . \quad (4)$$

In this equation $k_1 = \frac{c_1}{I_0}$ and $k_2 = \frac{c_2}{L_0}$. In the steady state from which we start $x(t) = 1$. So $x(o) = 1$.

If the elements of X serve to build up a new substance Y, which is not radiosensitive and if we have to do with monomolecular reactions, then

$$\frac{dy(t)}{dt} = -J_0\,y(t) + J_0\,x(t-\tau_3) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

It will be clear that the above-mentioned equations only obtain if the reactions are reversible. In order to deal also with irreversible effects, we must assume that these will occur if the relative concentration of X reaches a critical value 1—A.

Although the new equations suffice to explain qualitatively all FORSSBERG's experiments as well as the other oligo-phasic reactions which were already treated in the author's previous papers, there is still another point on which the theory can be extended. This concerns the relaxation-times τ_1 and τ_2.

If the object is irradiated during a certain time T with an intensity i, then, according to equation (3) there would happen nothing to the elements of X during the time τ_1. After the time τ_1 the dissimilation-coefficient would suddenly jump towards $I_0 + c_1 i$ and keep this value during a time T, in order to jump back towards the original value I_0. To the assimilation-coefficient something similar would occur after the time τ_2.

If we are dealing with large numbers of ions and elements we can imagine that these events do not occur discontinuously but (quasi-) continuously, in other words, that the dissimilation-coefficient begins to develop without any latency-time, but gradually reaches the enlarged

value, in order to return towards the original value also gradually after the irradiation has been finished. The same thing may happen to the assimilation-coefficient, with another time-factor however. Let us try to realize, what may occur. In the first place the concentration of the formed ions will not suddenly jump towards a new value, when the irradiation begins, but it will gradually increase. In proportion as there are formed more ions, more will be neutralized or, with higher objects will be removed. One may suppose that, analogous to purely physical events, the concentration of formed ions will tend to a certain limit-concentration, which, in a first approximation will be proportional to the intensity of the radiation.

This is, however, not the only possibility. One has to consider that the new-formed ions can only break down or build up an element of X if they have a certain activating-energy, while moreover other factors like collisions at determined sites of molecules or cells may be necessary to effect the reactions. Particularly new syntheses may last a relatively long time. Such events have already been known to exist in anorganic nature, for instance with the chemical reaction $H_2 + J_2 \rightleftarrows 2HJ$.

If one calculates the number of collisions between H_2 and J_2 molecules, one finds a number of about 10^9/sec. The equilibrium would establish itself after 10^{-9} sec. It only does so, however, after about 2 hours.

If one realizes these possibilities it seems impossible to characterize the events of metabolism mathematically, the different factors being unknown. Still it is more or less possible to make a fair approximation if one considers the following:

According to the above the new-formed ions will enlarge the dissimilation-coefficient gradually from I_0 to $I_0 + c_1 i$. I_0 is proportional to the concentration of the dissimilating ions before the irradiation, while $c_1 i$ is proportional to the final increase of this concentration during the irradiation. Now let us assume that, of the new-formed ions a part $a_1(\theta)d\theta$ are beginning their activating work between the times θ and $\theta + d\theta$. This means that $a_1(\theta)$ is the probability that a newformed ion will begin its activating work after the relaxation-time θ. Let all relaxation-times be possible, with a mean-value τ_1, independent of the intensity and be $a(0) = 0$ and $a(\infty) = 0$.

That all relaxation-times are possible, is expressed by

$$\int_0^\infty a_1(\theta)\,d\theta = 1 \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (6)$$

From the fact that the mean-value of all relaxation-times is τ_1, it follows that

$$\int_0^\infty \theta a_1(\theta)\,d\theta = \tau_1 \ldots\ldots\ldots\ldots\ldots\ldots \quad (7)$$

The function which satisfies all these conditions is the distributic 1-function of Poisson

$$a_1(\theta) = A_1\,\theta^{m_1-1}\,e^{-n_1\theta} \quad \ldots\ldots\ldots\ldots \quad (8)$$

where m_1 and n_1 are constants.

Substituting (8) in equations (6) and (7) we find

$$a_1(\theta) = \frac{{n_1}^{n_1\cdot\tau_1}\,\theta^{n_1\tau_1-1}\,e^{-n_1\theta}}{\Gamma(n_1\tau_1)} \quad \ldots\ldots\ldots \quad (9)$$

If now the »equation of metabolism» be

$$\frac{d\xi(t)}{dt} = -\{I_0 + I(t)\}\,\xi(t) + \{L_0 + L(t)\}\,\varrho(t) \quad \ldots\ldots \quad (10)$$

then generally

$$I(t) = c_1 \int_0^t i(t-\theta)\,a_1(\theta)\,d\theta \quad \text{and} \quad L(t) = c_2 \int_0^t i(t-\theta)\,a_2(\theta)\,d\theta \quad \ldots \quad (11)$$

In these equations the intensity i(t) may be a function of the time as well.

In case the irradiation has a constant intensity during the time T, we reduce

$$I(t) = c_1 i \int_0^t a_1(\theta)\,d\theta = c_1 i\,\frac{\Gamma_{n_1 t}\,(n_1\tau_1)}{\Gamma(n_1\tau_1)} = c_1 i\varphi_1(t) \quad \text{and} \quad L(t) = \\ = c_2 i\varphi_2(t) \ldots\ldots o < t < T \quad \ldots\ldots\ldots \quad (12)$$

Herein $\varphi_1(t)$ and $\varphi_2(t)$ are functions which, between $t = 0$ and $t = \infty$ increase sigmoidally from $0 \rightarrow 1$.

If the irradiation is stopped after the time T, then it follows from (11)

$$\left.\begin{aligned} I(t) &= c_1 i \int_{t-T}^t a_1(t)\,d\theta = c_1 i\,\{\varphi_1(t) - \varphi_1(t-T)\} \\ L(t) &= \qquad\qquad c_2 i\,\{\varphi_2(t) - \varphi_2(t-T)\} \end{aligned}\right\} \; t > T \quad \ldots\ldots \quad (13)$$

Indeed, for $0 < t < T$, $i(t) = i$ and for $t > T$, $i(t) = 0$.
So for $0 < \theta < t - T$, $i(t-\theta) = 0$ and for $t - T < \theta < t$, $i(t-\theta) = i$.

We may therefore describe the changing of the number of elements of X during and after the irradiation by the following equations

$$\left.\begin{aligned} &\frac{d\xi_1(t)}{dt} = -\{I_0 + c_1 i\varphi_1(t)\}\,\xi_1(t) + \{L_0 + c_2 i\varphi_2(t)\}\,\varrho(t) \ldots\ldots 0 < t < T \\ &\text{and} \\ &\frac{d\xi_1(t)}{dt} = -[I_0 + c_1 i\,\{\varphi_1(t) - \varphi_1(t-T)\}]\,\xi_2(t) + \\ &\qquad + [L_0 + c_2 i\,\{\varphi_2(t) - \varphi_2(t-T)\}]\,\varrho(t) \ldots\ldots t > T \end{aligned}\right\} \quad (14)$$

In the special case that one starts from the steady state and that the concentration of the reserves or new-matter is not influenced during the entire process, we can reduce (14) to

$$\left.\begin{aligned} \frac{dx_1(t)}{dt} &= -I_0\{1+k_1 i\varphi_1(t)\}\,x_1(t)+I_0\{1+k_2 i\varphi_2(t)\} \quad . \quad 0<t<T \\ &\text{and} \\ \frac{dx_2(t)}{dt} &= -I_0[1+k_1 i\{\varphi_1(t)-\varphi_1(t-T)\}]\,x_2(t)+ \\ &\quad +I_0[1+k_2 i]\,\varphi_2(t)-\varphi_2(t-T)\}] \quad . \quad . \quad . \quad . \quad . \quad t>T \end{aligned}\right\} \quad (15)$$

The difference between the first and the second conception of the dissimilation and assimilation-coefficient can be understood from fig. 1).

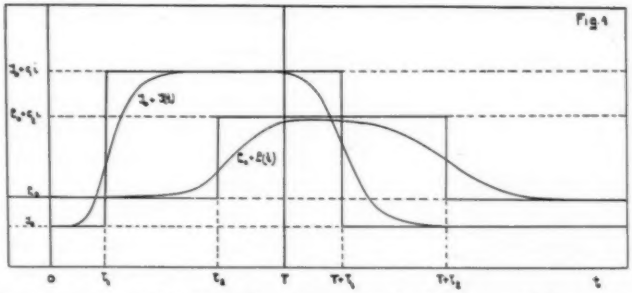

Fig. 1. Development of the dissimilation- and assimilation-coefficient according to the first simplified and the second generalized conception.

If τ_1 is small and n_1 is large, the first begins to rise very soon and then quickly. If τ_2 is large and n_2 is small, the latter begins to rise later and then more slowly. For $n_1 = \infty$ and $n_2 = \infty$ the course becomes that of the discontinuous coefficients of equation (3).

If the elements of X serve to construct a new substance Y and if one assumes that also these events occur after any relaxation-times then for Y generally obtains:

$$\frac{dy(t)}{dt} = -J_0 y(t) + J_0 \psi(t) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

in which

$$\psi(t) = \int_0^t x(t-\theta)\,a_2(\theta)\,d\theta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

Of course the new equations (15) and (17) are approximations as well. Qualitatively they are not better than the first obtained (4) and (5).

4. I shall now test the theory to the experiments of A. FORSSBERG on the fungus-cell Phycomyces Blakesleeanus, which reacts already to extremely small dosages of Roentgen-rays with characteristic changes of its growth-rate. From the extensive report (1943) of FORSSBERG's experiments we see that there are two groups. A first series relates to the irradiation of the cell for a short time with different intensities. It appears that:

1. The fungus-cell is extremely sensitive and reacts already perceptibly to a dose of 0.0005 r. Yet there are individual differences in the sensitiveness, which show in a somewhat divergent course of the changes in the growth-rate.

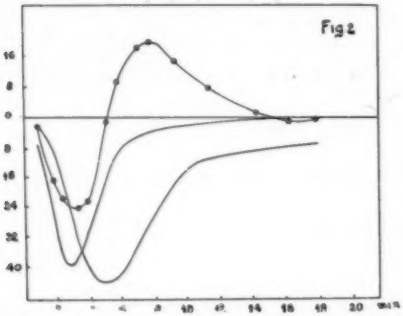

Fig. 2. 3 experimental curves of FORSSBERG with different types of cells.

Ordinates: Percentual changes in the growth-rate.

Abscissa: Time in min.

Dose 2r, intensity 15 r/min., irradiation-time 8 sec.

(FORSSBERG, A. Acta Radiol. Suppl. XLIX 1943.)

2. The changes in the growth-rate are reversible up to a dose of about 1,000 r. For larger doses there are irreversible changes.

3. The changes in the growth-rate begin to occur only after a latency-time of about 40 sec. at 20 C. This time appeared constant at an intensity-interval from 1 to 2,000. For the rest the latency-time appeared to be dependent on temperature, while likewise it was found that the latency-time is shorter in proportion as the normal individual growth-rate of the cell is greater.

4. The course of the changes in the growth-rate is as follows (fig. 2): After the latency-time there is always first a phase during which the growth-rate diminishes more and more, in order to increase considerably after a minimum has been reached. For many cells the normal growth-rate is exeeded and a phase originates in which the growth-rate increases. After having reached a maximum, the growth-rate gradually returns to the original value. There are also cells, however, with which the phase of increased growth-rate fails to appear and the latter, after having reached the minimum, first rises rapidly, then slowly increases to the normal value. So in this case the course is mono-phasic. In some cases, when the course is mainly diphasic, the first period is followed by a second very weak period. The latter only manifests itself clearly, when a first fairly weak retardation-phase is followed by a comparatively strong stimulation-phase.

5. With experiments on one and the same cell both the amplitude of the minimum and that of the maximum growth-rate appear to increase with increase of the intensity. Both magnitudes, however, tend to limit-values. On application of dosages above 1 r there are no obvious modifications of the effect.

6. If with constant intensity the irradiation-time is continuously prolonged, the moment at which the growth-rate becomes minimal moves more and more to a certain limit-value. Also the amplitude continuously increases with this minimum and it likewise tends to a limit.

7. If the irradiation is prolonged a very long time (20 min.), a monophasic course originates. After the growth-rate at the end of the latency-time has decreased to a certain minimum, a new rise asserts itself and the growth-rate stabilizes at a new, generally lower level. For increasing intensity this level will be lower.

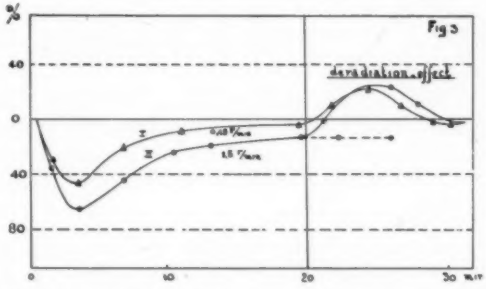

Fig. 3. 2 experimental curves of FORSSBERG with different intensities for long-lasting irradiation (20 min.) and deradiation effect.

1. 0.15 r/min. II 1.50 r/min.

The dotted line shows the stabilization if the irradiation is continued longer than 20 min.

(FORSSBERG, A. Acta Radiol. Suppl. XLIX 1943.)

If the irradiation is stopped, a rise over the normal value up to a maximum occurs, after which a decline to the original normal value asserts itself (fig. 3). This effect has been already observed by BLAAUW and VAN HEYNINGEN (1925), who called it the »deradiation-effect».

Apart from the above-mentioned ones FORSSBERG has carried out another series of experiments which concerned the causes of the effect and the localization in the cell. He has discovered for instance that:

1. The primary reaction takes place in the wall of the cell and thence propagates to a certain area, the growth-area, which is situated just under the sporangium-capsula.

2. The propagation-velocity could be determined and appeared to be about 1.7 mm/sec. independent of the temperature.

3. In the growth-area to all seeming a coupling to certain receptors occurs, which leads to the visible phenomena of growth.

4. Whether the growth-area was also irradiated or not had no influence on the biological effect.

5. The quantitative result of the reaction is independent of the size of the irradiated cell-volume, but depends on the density of the ionization. Etc.

5. From the above-mentioned series of observations about the causes of the various effects and the localization in the cell it follows that we have to conceive things as follows:

In the cell-wall there is a radio-sensitive substance X the reaction of which is determined by the equations (14) or by the simplified one (8). For reasons of simplification we may use the latter.

This substance X, or at least something proportional to the concentration of X, is conducted to the growth-area where there is another substance Y. For the building-up of Y the reserve-material is among other things determined by the concentration of X. Before the experiment, provided Y is like X considered to be in a steady state, obtains for Y

$$\frac{d\eta(t)}{dt} = -M_0\eta(t) + N_0\xi_0, \quad \eta(t) = \eta_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

It now appears from the experiments that the substances of the growth-area are not radio-sensitive. If therefore X is modified by the irradiation, the equation for Y will become, in simplified form,

$$\frac{d\eta(t)}{dt} = -M_0\eta(t) + N_0\xi(t-\tau_3) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

in which τ_3 is the time needed to propagate X or some other effect of X. In the same way another substance may be imagined, coupled to Y etc.

Ultimately the chain ends with a biogenic matter U, the dissimilation-coefficient P_0 being negligible against the assimilation-coefficient Q_0, in this case better called growth-coefficient. The latter matter U increases with a rapidity which is proportional to the concentration of the immediately preceding reserve-matter.

If the reserves which build up X are so great, that their concentration does not change during the experiment, notwithstanding the heavier charge, then always obtains $\varrho(t) = \varrho_0$ and if by careful preparation and by maintaining constant all possible circumstances, the dissimilation, respectively assimilation-coefficients become constant, the matter X and consequently all following substances Y, Z ..... will get into stationary conditions. Except the last one U, because this matter, on account of the smallness of its dissimilation-coefficient P_0, only reaches the steady state at a moment much and much later than the end of the experiment.

Let the thus-generated resting-concentrations be respectively ξ_0, η_0, ξ_0 etc. then

$$\xi_0 = \frac{I_0 \varrho_0}{I_0} \text{ and } \eta_0 = \frac{N_0 \xi_0}{M_0} \quad \ldots\ldots\ldots\ldots (20)$$

If we introduce the relative concentrations $y(t) = \frac{\eta(t)}{\eta_0}$ and $x(t) = \frac{\xi(t)}{\xi_0}$, then we obtain, as before

$$\frac{dx(t)}{dt} = -I_0 \{1 + k_1 i(t-\tau_1)\} x(t) + I_0 \{1 + k_2 i(t-\tau_2)\} \quad \ldots (21)$$

and

$$\frac{dy(t)}{dt} = -M_0 y(t) + M_0 x(t-\tau_3) \quad \ldots\ldots\ldots\ldots (22)$$

etc.

Now we may see whether these equations can describe the observed reactions. As for the changes of the relative concentration of the substance X by an irradiation during a time T, we find the following course:

After the time τ_1 during which nothing seems to happen, the rel. conc. of X decreases during a time equal to the irradiation-time T, to the value $x(\tau_1 + T)$, in order to rise afterwards till the moment $t = \tau_2$. If k_2 is large enough, subsequently an increase over the normal value 1 asserts itself. From the time $t = \tau_2 + T$ the rel. conc. of X decreases again to the original value 1. So a diphasic curve originates.

The amplitude of the stimulating-phase $S = x(\tau_2 + T)$ will depend on the magnitude of the multiplying constants k_1 and k_2. The smaller k_2 is with respect to k_1, the smaller S will be. If $k_2 \ll k_1$ the stimulating-phase will even fail to appear and the course will become monophasic.

Viewing the course of the rel.conc. of Y, which in a certain sense reflects the course of X, we see that the elementary integrations produce a similar diphasic or monophasic course depending on k_1 and k_2. The reaction sets in after a latency-time $\tau_1 + \tau_3$.

There are however a few typical differences. The minimum of X appears at the time $t = \tau_1 + T$, the minimum of Y, however, is not reached at the time $t = \tau_1 + \tau_2 + T$, as one might expect, but later. Besides, the amplitudes of the rel. conc. of Y are smaller than those of X, so that the curve obtains a shape which wonderfully well resembles the one obtained from the experiment.

Advancing another step and observing the reactions of a subsequent substance Z, we find that the latter possesses the same properties to an even enhanced degree.

In fig. 4 one can see an example of the course of X, Y and Z, with negligible irradiation-time and in case k_1 and k_2 are about equal; in fig. 5 k_2 is small against k_1.

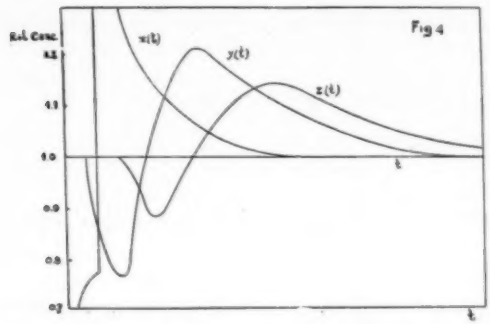

Fig. 4. Course of rel. conc. of X, Y, and Z during and after an irradiation of negligible time. $k_1 \backsim k_2$.

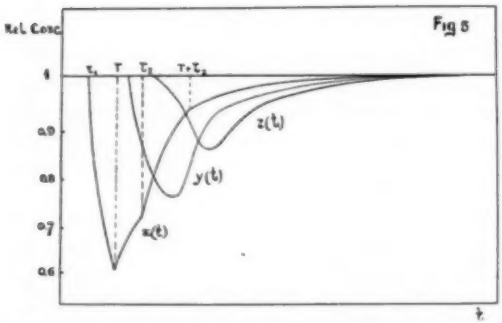

Fig. 5. Course of the rel. conc. of X, Y and Z during and after an irradiation of relatively short time T. $k_1 \ll k_2$.

In some cases the experimental curve, after having reached its maximum, will not decline asymptotically to the original value, but the first period is followed by another very weak one. This slight discrepancy between theory and experiment can easily be explained. For FORSSBERG discovered that this phenomenon asserts itself when the stimulating-phase is very manifest. It has been assumed, that the reserves R of X do not appreciably change in the course of the experiment, so that we could always put $\varrho(t) = \varrho_0$. In the stimulating-phase, however, they are especially heavily charged and it is therefore probable that the very weak second period owes its existence to the fact that these reserves cannot stand the heavy charge without more ado.

Another characteristic difference between the primary reaction of X and that of Y respectively Z etc. is the following, which likewise produces a concurrence of theory and experiment.

If we consider the minimum of x(t), so

$$x(\tau_1 + T) = \frac{1 + Ie^{-I_0(1+I)T}}{1 + I} \quad \text{for } T < \tau_2 - \tau_1, \text{ and } I = k_1 i$$

as a function of the intensity i, then for increasing i this minimum value will tend to zero, in other words, the minimum can reach any value between 1 and 0, if only we make i large enough. The experiment (fig 6) yields the result, that for increasing i the minimum decreases indeed, but only to a certain limit. The calculation of the minimum of Y, however, produces exactly the same phenomenon, for we obtain that the

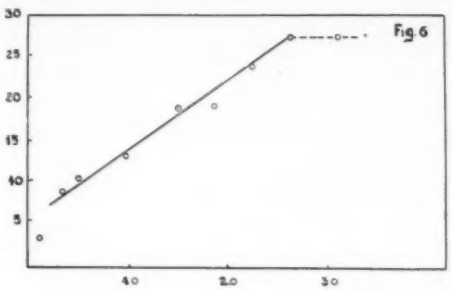

Fig. 6. Experiment of FORSSBERG. Changes in the inhibition-amplitude of the growth-rate for ever-increasing doses.

Ordinates: Extreme decrease of the growth-rate, expressed in percentage of the normal one.
Abscissa: log (1,000 x dose in r).
(FORSSBERG, A. Acta Radiol. Suppl. XLIX 1943.)

minimum of Y is reached after a time t_1, which for increasing i tends to the limit $t\,\infty$:

$$t_\infty = \tau_1 + \tau_2 + T + \frac{1}{M_0 - I_0} \lg\left[1 + \left(\frac{M_0}{I_0} - 1\right) e^{-M_0 T}\right]. \quad . \quad . \quad . \quad (23)$$

While for increasing i, y_{min} continuously decreases to the limit-value

$$y_{min,\,\infty} = 1 - \left[1 + \left(\frac{M_0}{I_0} - 1\right) e^{-M_0 T}\right]^{\frac{-1}{\frac{M_0}{I_0} - 1}} \quad . \quad . \quad . \quad . \quad . \quad . \quad (24)$$

In case t_∞ should be greater than $\tau_2 - \tau_1 + \tau_3$, after which the enhanced assimilation-coefficient asserts itself, both limit-values are not even reached.

Keeping the intensity constant, but increasing the irradiation-time up to and above the time $\tau_2 - \tau_1$, we of course find that the stimulating-phase will be more and more suppressed, if the irradiation-time continues to increase. For very long irradiation-times the growth-rate will become stabilized at a level, which according to the theory is determined at the relative value

$$\frac{1 + k_2 i}{1 + k_1 i},$$

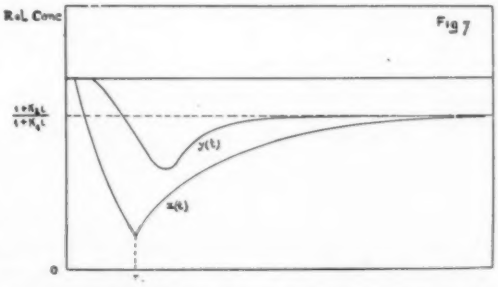

Fig. 7. Course of the rel. conc. of X and Y during an irradiation of infinitely long time $k_1 < k_2$.

After the rel.conc. of X, Y etc. has at first decreased to a certain minimum, it subsequently increases gradually to this value (fig. 7, compare fig. 3). The course is therefore in accordance

again with the experiment. It appears at the same time that for the fungus-cell examined $k_2 < k_1$, for the level is lowered in the accomodated condition and with increasing i it becomes ever lower.

Furthermore we have the deradiation-effect. This is also explained by the theory.

After adaptation has been achieved, for X the equation holds

$$\frac{dx_0(t)}{dt} = -I_0(1 + k_1 i)\, x_0(t) + I_0(1 + k_2 i) \quad . \quad . \quad . \quad . \quad . \quad (25)$$

with

$$x_0(\infty) = \frac{1 + k_2 i}{1 + k_1 i}.$$

If the irradiation is ceased, we first obtain (after τ_1 sec.)

$$\frac{dx_1(t)}{dt} = -I_0 x_1(t) + I_0(1 + k_2 i) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (26)$$

and after τ_2 sec.

$$\frac{dx_2(t)}{dt} = -I_0 x_2(t) + I_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (27)$$

Hence it follows as a matter of fact, that after the cessation of the irradiation an increase of the rel. conc. of X ensues, which is followed by a decline towards the original value 1. A similar sequence holds for Y respectively Z etc. (fig. 8, compare fig. 3).

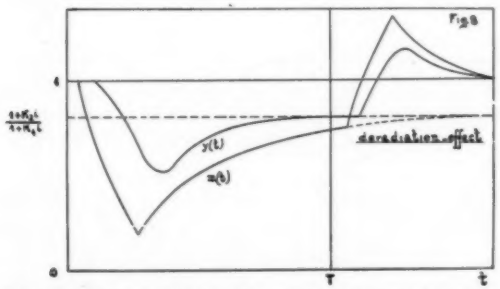

Fig. 8. Course of the rel. conc. of X and Y during and after an irradiation of relatively long time T and deradiation-effect.

The fact that we sometimes see the experimental curve dip just below the normal, in order to revert afterwards to the value 1, can again be explained in this way, that by the high charge the concentration of the reserves cannot be put exactly equal to ϱ_0, but that this heavier charge diminishes it temporarily a little.

Finally a further word may be said about the fact that with doses of over 1,000 r irreversible effects become observable. It seemed in every respect remarkable, that with heavy doses which approach this value, all at once irreversible changes originated, while the biological effect

ha long before reached a definite limit-value. This phenomenon is fo ıded on the fact that with the primary reaction a certain critical an ılitude is being passed, where the stable circumstances become meta-sta le. Since the amplitude with the secondary reactions of Y, Z etc. te ls to a limit for increasing i, this critical amplitude does not clearly sh v here.

. The theory, as it has been developed now, not only gives a comple e explanation of FORSSBERG's experiments, but also of the many oth r oligophasic reactions which occur after roentgen-irradiation. I ma omit a full extent of these reactions, as they already followed from the author's previous equation. Other important conclusions, like the rela ionship to the hit-theories and the consequences for the manner of distributing the different doses in therapy, which would make this communication too long, will be published in a monograph, together with a more extensive mathematical treatment. This monograph will also contain a new theory of the local phenomena of excitation in nerve, caused by electric currents. These have been studied very thoroughly during the last century and they show a great analogy with the reactions in cells and tissues after roentgen-irradiation. This may not cause any surprise. While Roentgen-rays are always forming ions, electric currents will displace them. In both cases there will be local changes in the concentration of different ions.

If one applies the above theory to the numerous exactly-studied phenomena, which occur, if one sends currents of all kinds of forms through part of a nerve, then these phenomena can be explained completely by the theory and even more completely than by any other theory.

It is clear that the author is considering this as an important argument for the rightness of his ideas.

SUMMARY

The author communicates a further development of his theory of biological reactions caused by Roentgen-rays. With the aid of the proposed »equation of metabolism» it becomes possible to give a full explanation of the experiments of A. FORSSBERG on Phycomyces Blakesleeanus.

ZUSAMMENFASSUNG

V rfasser veröffentlicht eine weitere Entwicklung seiner Theorie der biologischen Reakt onen, verursacht von Röntgenstrahlen. Mit Hilfe der vorgeschlagenen Stoffwechselgleich ng gelingt es die Experimente A. FORSSBERGS mit Phycomyces Blakesleeanus völlig zu erklären.

RÉSUMÉ

L'auteur communique un nouveau développement de sa théorie des réactions biologiques, causées par des rayons de Roentgen. Avec l'aide de l'équation de métabolisme proposée, il devient possible de donner une explication complète des expériments de A. Forssberg sur Phycomyces Blakesleeanus.

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FROM THE BISPEBJERG HOSPITAL, ROENTGEN DEPARTMENT (CHIEF: CHR. I. BAASTRUP)

DIAGNOSIS OF ECTOPIC PREGNANCY BY HYSTEROSALPINGOGRAPHY[1]

by

Børge Nielsen.

As a rule the diagnosis of ectopic pregnancy is based on the history, objective signs, and a few laboratory findings. Roentgen examination, on the other hand, is seldom used. In typically acute cases, involving severe intra-peritoneal hæmorrhage, one can seldom use a diagnostic procedure which always requires some time, but in cases of less threatening hæmorrhage, particularly if there have been repeated minor hæmorrhages, a Roentgen examination of the abdomen may be useful, especially to ascertain the presence of free fluid (3). In cases where the pregnancy remains undisturbed for some length of time, it is of diagnostic importance to be able to demonstrate a normal uterine cavity by hysterosalpingography beside the Roentgen picture of the foetus. Finally, one may chance to find an ectopic pregnancy at a very early stage when performing hysterosalpingography for other reasons.

However, after the disaster has occurred, most cases follow a fairly slow course, presenting themselves as gynæcological affections of a more or less definite nature. The literature contains a few reports on hysterosalpingography as an aid in diagnosis in such cases, but the method is not widely used.

In DYROFF's opinion (1) the roentgenological picture presented lacking filling of the pregnant salpinx and simultaneous atony of the uterus.

SCHNEIDER & EISLER (5) also considered this picture characteristic of the affection, barring intra-uterine pregnancy at a very early stage or incomplete abortion. In addition, they describe a number of pictures demonstrable when the iodized oil gives different filling of the pregnant salpinx which is partly filled by the mole and blood clots. In their opinion a segmental irregular filling of an obstructed salpinx, or escape of small drops of oil in or above the hæmatoma, or the filling of a fat space between the hæmatoma and the wall of the salpinx, present

[1] Submitted for publication, Oct. 16, 1946.

unquestionable, characteristic pictures on which the diagnosis may be based. Their material consists of 10 cases.

POPOVIĆ & SMOKVINA (4) describe the same pictures as SCHNEIDER & EISLER, but consider some of the changes in the salpinx to be due to spasms. They report 23 cases of ectopic pregnancy, but only a small number of them appear to be proven by operation.

All the authors mentioned fail to give an accurate statement of the number of times they have come across the various pictures, and the same applies to MATHIEU (2) who has a high opinion of this method which he considers to give practically 100 per cent. correct diagnoses.

On the other hand, SCHULTZE (6), who appears to have the largest material at his disposal, is very critical as to the result of the examination. Only 13 of his 25 cases exhibited a flow of the contrast material into the pregnant salpinx, and he states that he has never observed anything interpretable as a picture of the ovum. In addition, he thinks that most of the findings described by the other authors may be present also in cases of commonplace inflammatory conditions, and therefore greatly doubts the diagnostic certainty. The Roentgen result was correct in only half the 18 cases in which ectopic pregnancy had not been suspected or the diagnosis was doubtful. Still, he mentions the occurrence of striking changes in the Fallopian tube and in the picture taken 24 hours later, changes which, however, are too inconstant to form the basis of a satisfactory diagnosis. Particular importance must be attached to SCHULTZE's opinion, partly because of his wide experience, and partly because he appears to have published the most recent report on the subject.

Writer's Investigations

Below a report is given of the result of hysterosalpingography in 25 cases exhibiting or suspected of ectopic pregnancy. All diagnoses have been confirmed by operation or protracted clinical observation.

Before passing on to the material, the writer will briefly touch upon the pathological aspect. Only the roughest changes are of interest. Let it be mentioned at once that neither the literature nor the writer's material contain a case of ovarian or abdominal ectopic pregnancy, and this picture is therefore unknown. Probably there will be a mass in the pelvis and the salpinx on the same side will sink into the hæmatoma and therefore be obstructed and dilated. The picture will, however, hardly be characteristic, and these rare cases must be kept in mind as a possibility about which hysterosalpingography fails to afford definite information. Usually, however, the ovum will become nidated somewhere in the salpinx where its growth will cause dilatation of the lumen.

But the latter is filled by the ovum, the mole, or blood clots, leaving, however, a narrow space under the wall of the salpinx. The thing to do is to make the contrast material run into this space, an attempt in which one may succeed to a different extent. At times it is closed, so that only a small portion of the salpinx is filled, and finally the contrast medium may not run into the salpinx at all. The filled part of the salpinx may help one to localize the site of implantation, but apart from that there does not appear to be a possibility of obtaining further information. It is hardly possible in all cases to decide whether it is a question of tubal abortion or rupture. The former may though sometimes be demonstrable on some of the films.

Technique

In order to obtain the best possible result, it is necessary to dwell upon a few details of technique. All the authors mentioned above have used iodized oil as a contrast medium. Our satisfactory results must presumably be ascribed mainly to the use of perabrodil. The advantage of water soluble contrast media above oil is most strikingly apparent when it is a question of obtaining a flow of the contrast medium into narrow crevices. We employ the ordinary 35 per cent. solution without adding any anæsthetic fluid.

Secondly, one must make several films in different projections. Preferably one must be able to follow the contrast medium spreading in the pregnant salpinx, and it is also important to watch its absorption. It is true that the very first films are often sufficient, affording all that is obtainable, but at times it is difficult to interpret the picture on account of an ample flow of contrast medium into the peritoneal cavity through the normal salpinx, and now and then the material trickles slowly into the space. One may have to repeat the injection, but generally the best possible filling is obtained by simply closing the apparatus while the first films are being developed.

The Roentgen Aspect of Ectopic Pregnancy

At first sight the films which may be obtained in cases of tubal pregnancy are extremely varied.

Before proceeding further, mention should be made of a few details of slight or no diagnostic significance.

As mentioned above, atony of the uterus has been attributed with importance in cases of lacking flow into a salpinx. This phenomenon is, however, said to be rare. Among his material of 25 cases SCHULTZE only found atony as in pregnancy in 6 and slight atony in 9. In the

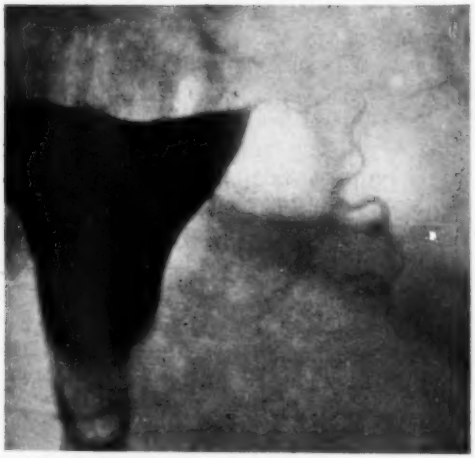

Fig. 1 a.

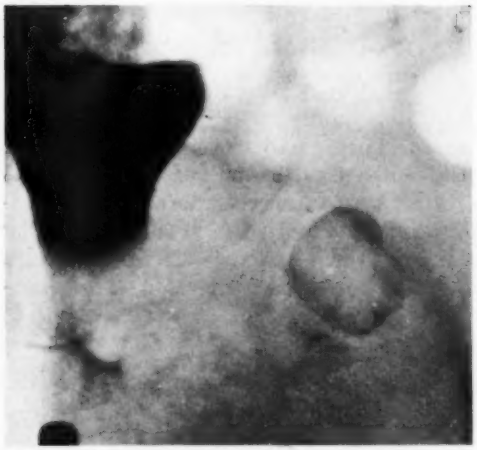

Fig. 1 b.

present material of ectopic pregnancies atony as in pregnancy was not observed, and only in 2 cases could the uterus be described as hypotonic. When faced with an atonic uterus without a simultaneous characteristic picture of the salpinx, one must sooner expect an intra-uterine pregnancy at a very early stage or an abortion than ectopic pregnancy.

Furthermore, a shift of the uterus which may be caused by the hæmatocele is of course of no direct diagnostic importance, but this finding may serve to correct the diagnosis made by gynæcological examination.

The same applies to masses in the pelvis demonstrable by the contrast medium in the peritoneal cavity. We have not performed systematic pelvigraphy and have therefore seldom observed the masses by that method. In one case exhibiting a large hæmatocele there was a strikingly irregular picture of the contrast medium on a level with Douglas' cul-de-sac.

Lastly, it is worth mentioning the filling of the non-pregnant salpinx which, according to SCHULTZE, is usually abnormal. In his material it appears, however, often to be a question of an uncharacteristic interruption of the filling. The cause may perhaps be sought in his use of iodized oil. In the writer's material, at any rate, the non-pregnant salpinx was found to be normal and palpable in 9 of the 12 cases. Two cases revealed an ordinary sacto- or pyosalpinx

an one a sactosalpinx ca sed by the fact that th ampullar portion had su k into the hæmatoma an become obstructed.

The only feature of di gnostic importance is th picture of the preg- na t salpinx. The findings fal into 4 rather sharply de arcated groups.

(A). The first group co prises the cases which in ur opinion present the mole as a filling defect, the space around it being more or less occupied by contrast medium. The first portion of the salpinx is normal or dilated into the form of a mallet, and the shadow then continues as a thinner stripe, usually forming part of an arc. The following films will show the contrast medium spreading, and a somewhat varied picture may be obtained. Some cases exhibit a circular, semicircular, or oval, homogeneous shadow, most dense in the peripheral areas where its outlines are sharp. Fig. 1 a reveals a non-dilated salpinx ending in the isthmus in a semicircular arc. The following film (1 b) presents a spot, the size of a six-pence, which gradually faded, but remained isolated. It is to be presumed that there was a flow of contrast medium only around the uterine pole of the mass in the tube. On Fig. 2 a the mallet shaped dilated salpinx is seen to end in a rather broad circular shadow, and on the next film the contrast

Fig. 2 a.

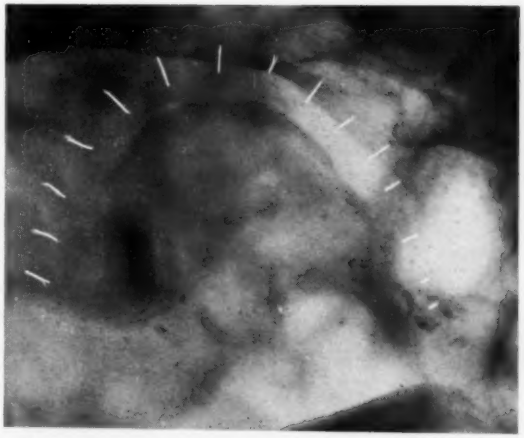

Fig. 2 b.

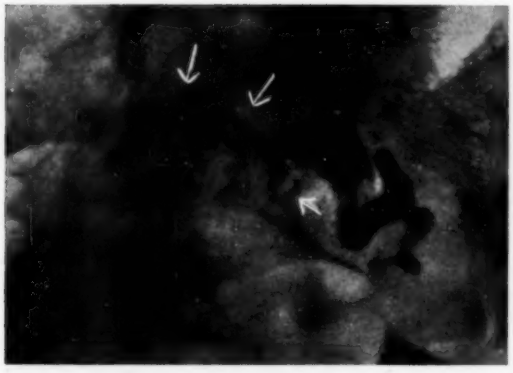

Fig. 3 a.

shadow spreads like a mantle, reminding of one half of an egg-shell.

In other cases the shadow is of an irregular spotty or striped pattern, though with a tendency to become more homogeneous later. On Fig. 3 a the dilated, winding tube ends in an oval rounded shadow. On 3 b there is still contrast medium in the stump, but more laterally the material has gathered, forming a patchy irregular pattern. Fig. 4 a represents a case with a hypermotile uterus which immediately ejected the perabrodil through the Fallopian tubes. The pregnant salpinx ends in the shape of a funnel, but it is partly covered

Fig. 3 b.

with irregular stripes and patches of contrast medium, more distinctly visible on 4 b, some time after the injection.

Presumably the difference between the pictures is due to the last-mentioned cases being representations of the surface of a hæmatoma, whereas the first ones revealed the space between intact vitelline mem-

b[illegible]nes and the wall of the salpinx. It is a common feature that the contrast shadow remains isolated, loosing itself very slowly, although the velocity of absorption differs somewhat. In the last-mentioned cases the perabrodil has no doubt also forced its way outside the lumen of the salpinx, a finding justifying a diagnosis of tubal abortion.

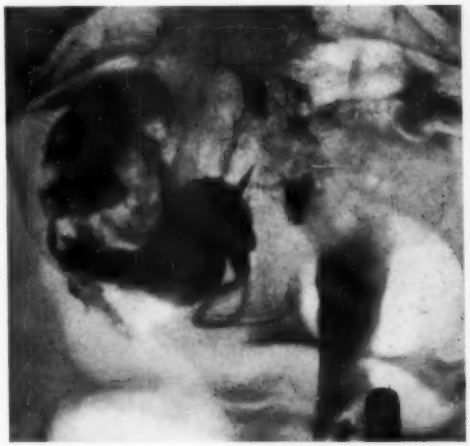

Fig. 4 a.

(B). Group B consists of cases in which the contrast medium does flow into the crevice, but in small amounts, and an actual filling defect cannot be demonstrated. One of these cases affords an illustration of the importance of continuing the observation some time after the injection. On the first film there was no flow into the pregnant salpinx, and when a typical sactosalpinx was found on the other side, the apparatus was removed. While the first films were being developed, there had, however, been flow of contrast medium into a slightly dilated part of the salpinx. By means of continued observation it was possible to watch the perabrodil proceeding in an irregular striped pattern.

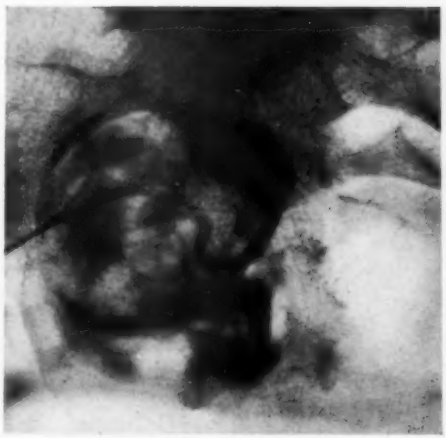

Fig. 4 b.

(C). The third group embraces the cases which revealed a flow of contrast medium into the salpinx, but not into the crevice. In all the cases the stump of the salpinx was of a striking shape. Fig. 5 exhibits a sudden semilunar dilatation in the isthmus. On Fig. 6 will be seen a mallet-shaped, dilated, slightly winding salpinx with a strikingly faint contrast shadow and a slightly striped pattern in the

Fig. 5.

Fig. 6.

Fig. 7.

Fig. 8.

distal part. Lastly, Fig. 7 presents a double outline in the distal part of the stump and a slight dilatation. At the same time one will observe a sickle-shaped shadow beside the uterus around a filling defect. In

this case it was, however, a question of contrast medium in the peritoneal cavity sucked over from the other side, a fact which was distinctly demonstrable on films made in the oblique position. It is worth mentioning that this mass had been misunderstood at the gynæcological examination.

(D). The last group consists of cases in which the contrast medium failed to flow into the pregnant salpinx.

Diagnostic Value. Differential Diagnosis. Ruling Out the Possibility of Ectopic Pregnancy

Obviously these different pictures are of different diagnostic value. As far as the last group is concerned, it is of interest only in so far as it is also of importance to be able to state that a diagnosis of ectopic pregnancy cannot be ruled out. Matters are more intricate when we come to group C. A simple interruption of the salpinx or mallet-shaped dilatation with a convex ending do not afford a proof. The cases in question did, however, exhibit peculiarities which the writer at any rate has not encountered earlier (cup-shaped dilatation, fading of the contrast medium at the distal end, and double outlines). Still, it is no doubt wise to exhibit some reservation in diagnosing these cases, until further experience has been accumulated.

On the other hand, the two first-mentioned groups, particularly group A, appear to give the diagnosis with very great accuracy. Considering, however, that the films only present quite rough anatomical features, consisting of a solid mass surrounded by a crevice, one cannot call the pictures pathognomonic, as similar changes may be imagined in conjunction with other conditions. This applies mainly to the rare new growths in the salpinx, but a tuberculous salpingitis with caseous degeneration may also cause difficulties. We lack personal experience in this respect.

It is more important to know whether certain more common diseases can be mistaken for ectopic pregnancy. One of our cases examined for ectopic pregnancy gave occasion to a suspicion that a large ovary adhering to the ostium of the Fallopian tube might give a simulating picture. At the end of the tube (Fig. 8) will be seen an oval, sharply outlined contrast shadow the inner structure of which appears to be chambered. On this film we made a diagnosis of cystic degeneration of the ovary, supporting the diagnosis on initial signs of a similar condition on the other side, but particularly on the fact that there was no typical retention of contrast medium on a level with the mass after the apparatus had been removed. By following the patient up for 6 months we have been able

to confirm the diagnosis, at least to rule out a diagnosis of ectopic pregnancy.

The practical significance of these possibilities must be decided by growing experience, but at the moment everything seems to indicate that the pictures described under the heading A, and possibly also B, are characteristic enough to give the diagnosis in practice.

Although the examination primarily aims at making a diagnosis of ectopic pregnancy, it has proved to be at least as useful in ruling out such a diagnosis. This fact does not appear to have been sufficiently emphasized earlier. When it is not a case of ectopic pregnancy, one may of course meet with all sorts of other changes, but the following features are of practical importance in making the diagnosis:

(1) Tubal pregnancy can be ruled out with certainty, if the salpinges are normal and passable. (2) With our present experience we are only able to interpret an uncharacteristic interruption of the flow into the salpinx to the effect that ectopic pregnancy cannot be ruled out. (3) When faced with a sactosalpinx, one must bear in mind that it may be caused by the salpinx sinking into the hæmatocele and therefore becoming obstructed (seen in one of our cases), and, as mentioned above, such a picture may be caused by ovarian pregnancy. In that case the diagnostic certainty is at any rate reduced.

(4) In addition, it has proved no rare occurrence that a diagnosis of intra-uterine pregnancy or abortion has been made. In such cases one has practically speaking arrived at the correct diagnosis, but theoretically one cannot rule out the simultaneous presence of tubal pregnancy, unless there is a flow of contrast medium through both salpinges.

Results of Hysterosalpingography in 25 Cases Suspected for Ectopic Pregnancy

It appears from the following table that half the cases of ectopic pregnancy exhibited the characteristic picture described under group A. In 11 out of the 12 cases the result afforded positive support to the diagnosis. In 1 case only did we have to restrict ourselves to stating that the possibility of ectopic pregnancy could not be ruled out. The same answer was also necessary in only 1 case of the second group, whereas tubal pregnancy could be ruled out in $^2/_3$ of the cases. Another and more satisfactory diagnosis could be made in the remaining cases.

12 Cases of Ectopic Pregnancy

(A) The mole demonstrated	6
(B) Only slight flow of contrast medium into the crevice	2
(C) No flow into the crevice. Striking picture of the salpinx	3
(D) No flow into the salpinx	1

13 Cases of Other Conditions

Diagnosis of tubal pregnancy ruled out by demonstrating normal, passable salpinges	8
Intrauterine pregnancy (1 with passable salpinges)	3
Abortion	1
Cystic degeneration of an ovary	1
Result questionable on account of lacking flow into one salpinx	1

Should a larger material present the same figures, this method of examination will, without doubt, become a factor of clinical importance.

Is There Any Reason to Use the Examination?

In the majority of cases one will probably be able to make the diagnosis after observation for a brief or long space of time wihout roentgenography, but it is often difficult to decide. According to MATHIEU (2), however, a correct diagnosis is passed in merely 50—70 per cent. of all cases. He adds that the percentage would fall perceptibly, if one included the cases which receive a diagnosis of tubal pregnancy and later prove to be false. Since the present material throws a light upon certain aspects of the uncertainty of the clinical diagnosis, the writer will deal with it in some detail below.

The case histories of both groups resemble each other, the main symptoms being menostasis, pain, and hæmorrhage[1], and typical as well as rather uncharacteristic descriptions are to be found in both groups. Palpable swellings were present in nearly all cases, but that was to be expected. In one case of ectopic pregnancy the diagnosis was difficult, because there was a swelling on the other side too, caused by an ovarian cyst. One instance in the group comprising cases not affected with ectopic pregnancy was clinically diagnosed as a hæmatocele, but in most of the cases the swellings have later been interpreted as enlargement of the ovaries. Strangely enough, there was no case of major inflammatory infiltrates. As the last-mentioned finding will hardly prove to be the case in a larger material, it means that the figures given above of normal passable salpinges must be presumed to be too high.

It is a well-known fact that the result of the Friedman-Schneider test does not decide the diagnosis. Since one might be liable to consider hysterosalpingography of special importance in those cases of ectopic pregnancy showing a negative reaction (in this material 3 out of 12), it is worth mentioning that the other group contained 3 with a positive reaction (intra-uterine pregnancies) causing great difficulties in making

[1] One case of ectopic pregnancy and 2 of the cases of intra-uterine pregnancy had no history of hæmorrhage. The third case of intra-uterine pregnancy had only bled slightly 3 weeks previously.

the differential diagnosis. In one of these cases the diagnosis was something of a surprise.

Furthermore, let it be stated that histological examinations of the endometrium do not always afford reliable results. The finding of decidua without villi or inflammation in only 2 of the 5 cases of ectopic pregnancy is a matter of no importance, but one case exhibited acute endometritis which was interpreted as the consequence of a past abortion, and delayed the correct diagnosis considerably. On the other hand, decidua without villi or inflammation were demonstrable in one case in which a certain diagnosis could not be arrived at. Possibly it was a question of incomplete abortion. This finding led to a laparotomy which failed to show anything abnormal apart from a fibroma in one side of the uterus and a small blood-filled cyst in one ovary.

It will be seen that the individual elements constituting the diagnosis are unreliable. It is, however, the picture in its entirety that matters. Since there was an indication for operation in all the cases of ectopic pregnancy as soon as the diagnosis was certain or extremely probable, one can form an opinion of the diagnostic difficulty by considering the pre-operative period of observation. On an average operation was performed in 13.5 days, not at all a brief stay in hospital. Hysterosalpingography was made on an average after a stay of 9.1 days. The use of the method is no doubt able to reduce the period of observation somewhat. Since it has, however, often been a question of differential diagnosis from inflammatory conditions, the significance of the method to early diagnosis becomes somewhat limited. In the other group the period of observation prior to hysterosalpingography was rather briefer (6.4 days); the longest periods were 7, 10, 13, and 22 days.

One might object that the diagnosis would at all events become clear after a sufficient period of observation. However, on the one hand one must demand that such observation be made in a surgical department, and on the other hand it is a fact that the clinical picture of certain other affections may resemble that of ectopic pregnany to the extent of leading to unnecessary laparotomies. Therefore, it must be considered useful to have a method which, like hysterosalpingography, speaks decisively for or against the diagnosis in the majority of cases.

The question then arises in which cases the examination should be used. In the writer's opinion it is not indicated by any particular clinical picture, but the selection of cases may be made according to two practical lines: Before the operation in cases not quite typical in order to avoid explorative laparotomies, and in doubtful cases in order to confirm the diagnosis within a reasonable period of observation.

Complications. Counter-indications

A factor of essential importance to the use of the method is the apparent absence of special discomfort or risk in these cases. However, the risk of inflammatory reactions, attaching to any hysterosalpingography, applies to these cases also. Therefore, it is necessary beforehand to rule out the possibility of acute inflammation, and moreover it is wise to stop the injection immediately upon finding a sactosalpinx.

As to the question of a possible rupture of ectopic pregnancy during the examination, none of the earlier authors have mentioned any complication. In one case of the present material the examination caused pains resembling those experienced by the patient earlier, and another patient felt unwell, but serious reactions were not seen. It is a matter of course that these patients should not be hysterographed without the chance of being immediately transferred to an operating room.

As it will not rarely be a question of intra-uterine pregnancy, it is appropriate to devote a few words to the risk of miscarriage. All are agreed that hysterography should not be performed with the sole purpose of making an early diagnosis or in definite cases of intra-uterine pregnancy. The question is, however, whether the mere possibility of the latter is a counter-indication. The literature contains quite a number of reports on hysterosalpingography performed on large numbers of pregnant women, without any miscarriage. Reviewing the case reports of such mishaps cited by SCHULTZE (6) one learns that in nearly all cases it has been a question of inadequate technique in the form of intra-uterine catheter or harmful contrast media. During the last 3 years we have hysterographed 4 cases of pregnancy without being aware of the diagnosis beforehand. Only one of the patients miscarried a few days after having left the hospital at her own request 3 days after the examination. At that late juncture the hysterosalpingography can hardly have been the cause. Although it is impossible to rule out the occurrence of such a mishap, the risk must be considered too slight to afford a counter-indication in the cases under discussion. Let it be mentioned, however, that the method should not be employed, if there is a possibility of imminent abortion in cases where one hopes to preserve the pregnancy.

Conclusion

As a result of the investigations one may state that hysterosalpingography will be able to speak decisively for or against the diagnosis in most cases suspected of ectopic pregnancy. It is to be recommended, particularly as it also appears to be unattended with risks other than those always attached to hysterosalpingography, and as the diagnosis is often difficult in such cases. Perhaps its greatest advantage is that

it may help to rule out the diagnosis in cases where the clinical examination and other diagnostic procedures erroneously indicate ectopic pregnancy. For that reason it is particularly useful as the last precaution before operation. It may, however, also be of importance in making an early diagnosis. Perabrodil is recommended as a contrast medium.

SUMMARY

The writer describes the Roentgen picture in 12 cases of ectopic pregnancy hysterosalpingographed with perabrodil and the findings in 13 cases of other affections, erroneously suspected for ectopic pregnancy. All the cases were confirmed at operation or through a long period of observation. Stress is laid upon the fact that this diagnostic procedure is at least as important in ruling out the possibility of ectopic pregnancy as in confirming the diagnosis. Mention is made of the uncertainty of the clinical diagnosis, and hysterosalpingography is recommended especially as a precaution before operating. It may, however, also be used as a means of arriving at an early diagnosis.

ZUSAMMENFASSUNG

Verf. beschreibt den Röntgenbefund bei 12 Fällen von Extrauteringravidität, an denen eine Hysterosalpingographie mit Per-Abrodil vorgenommen wurde, sowie die Befunde bei 13 Fällen von anderen Leiden, die irrtümlich als extrauterine Schwangerschaft verdächtig angesehen wurden. Sämtliche Fälle wurden durch Operation oder langdauernde Beobachtung bestätigt. Die Tatsache wird hervorgehoben, dass dieses diagnostische Verfahren für die Ausschliessung der Möglichkeit einer extrauterinen Schwangerschaft mindestens ebenso bedeutungsvoll ist wie für die Bestätigung dieser Diagnose. Die Unsicherheit der klinischen Diagnose wird erwähnt, und die Hysterosalpingographie empfohlen besonders als Vorsichtsmassregel vor der Operation. Doch lässt sie sich auch als Mittel zur Erzielung einer Frühdiagnose verwenden.

RÉSUMÉ

L'auteur décrit les images radiologiques de 12 cas de grossesses extra-utérines soumis à l'hystérosalpingographie au Perabrodil, ainsi que les constatations faites dans 13 cas d'autres affections, ou une grossesse ectopique avait été soupçonnée à tort. Dans tous, le diagnostic fut confirmé par l'opération ou par une longue période d'observation. Il souligne le fait que ce procédé diagnostique est pour le moins aussi important pour exclure la possibilité d'une extra-utérine que pour confirmer son existence. Il parle des hésitations du diagnostic clinique et recommande l'hystéro-salpingographie spécialement à titre de précaution pré-opératoire. On peut, néanmoins, aussi s'en servir comme moyen d'arriver à un diagnostic précoce.

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FROM THE ROENTGEN DEPARTMENT OF ULLEVÅL HOSPITAL, OSLO
(CHIEF: J. FRIMANN-DAHL, M. D.)

ON VENOGRAPHY OF THE LOWER EXTREMITIES[1]

by

J. Frimann-Dahl.

Venographic examinations may in normal cases give informations of appearance and course of the veins and reveal many details regarding *physiology* of the blood stream. No other method is capable of rendering such complete view of the course of the veins and of the blood circulation, also in pathologic conditions. Venography may thus in many ways be of inestimable value in the diagnostics. A retardation of velocity of the blood-stream may be disclosed, and roentgenograms after injection of contrast into the veins may with fair certainty show size and site of a thrombus.

In an earlier work (1935) the author has described the changes in velocity of the blood-stream in normal and in pathological cases. A considerable retardation of the blood-stream in the postoperative period was demonstrated. In the same work also a case of latent thrombosis of vena femoralis was reported, and diagnosed for the first time by roentgen examination.

Later many works on venography, dealing with the problem of thrombosis and particularly with the roentgen diagnosis of acute *thrombosis* have been published. Thus HELLSTEN and BAUER in 1940—41—42 presented an extensive material on this subject. The most important conclusions from these works are, that the spontaneous thrombosis most often is developed in the deep venous trunks of the calf, and that definite diagnosis of the lesion can be made by the aid of venography. Roentgenograms of the veins may even reveal positive findings in fairly many cases in which clinical determination of the diagnosis is impossible. These works have also thrown light on the condition that thromboses of the deep veins of the leg secondarily grow and spread upward toward the popliteal and femoral veins. It has further been shown that

[1] Read before the Northern Association of Medical Radiology at the meeting in Copenhagen, June 1946; submitted for publication Aug. 29, 1946.

an early diagnosis of thrombosis, when it is still localised to the calf of the leg, is highly important to the treatment.

These observations are fairly sensational, and in many respects give a different view of the question of thrombosis. Indeed, clinical observers have earlier, especially from 1930 and on, been aware of the fact that spontaneous thrombosis often arises in the calf. That the rate of frequency as shown by BAUER and HELLSTEN was so high, was however, not generally known. In his work BAUER gives the spontaneous thromboses beginning in calf of the leg at 97 % of the total number of cases. It will take us to far afield to discuss the details of venography in thrombosis, but it should possibly be taken into account that some of BAUER and HELLSTEN's cases, interpreted as thrombosis, in reality depends on abnormal venograms, caused by mistakes in the technique.[1] Even if that should be the case, I do not believe this capable of shaking the main point, namely that a great proportion of thromboses are developing in the calf. The classical view that most spontaneous thrombi were formed in the pelvic veins and in vena femoralis has thus been essentially altered. The modern view has revised the conception, not only of pathogenesis of thrombosis, but also of its treatment.

The following questions will today be of the greatest importance. Why do spontaneous thromboses often arise in the calf of the leg? and: May venography contribute to the illustration of these problems.

Approaching these questions, the roentgen department of Ullevål Hospital has made various venographical examinations, that will be reported in the following.

A total of several hundred venographies have been made, and the number of cases is rapidly increasing since the contrast again has been brought on the market.

A case of acute thrombosis, with a typical localization and distribution is firstly presented. (Fig. 1.) Here thrombi adherent to the vascular wall, partly obturating and flapping in the current are shown, both the deep venous trunks of the calf, and all the way from the ankle up to vena poplitea. By a follow-up examination the deep veins were quite obliterated and the blood stream passed through the saphenous trunk and collaterals. In this connection it shall be mentioned that our cases of chronic thrombosis are relatively numerous, and have increased in number, especially since lately many patients with chronic ulcers of the leg are sent for venographic examination.

The technique first used has been described by HAREIDE at a meeting of »Oslo Kirurgiske Forening» in 1943. He tried to obtain filling of the deep venous trunks of the calf by photographing the patient in a slanting position, feet down, at an angle of 15°—20°. It is an interesting obser-

[1] Cfr. LÖFSTED, S. and LINDE, P., Nord. Med. *31:* 1535, 1946.

Fig. 1. Fig. 2. Fig. 3.

Fig. 1. Shows acute thrombosis. Adherent, flapping and obturating thrombi pell-mell.
Fig. 2. Normal venogram, the extremity suspended above the table. Nearly all contrast passes through the deep veins. These are easily recognised, being companioned and supplied with valves.
Fig. 3. The leg is resting heavily upon the support with greater part of the weight on the calf. The passage through the deep venous trunks is interfered with.

tion that the veins thus undoubtedly filled very well. However, later we have changed the technique and are examining most patients, in whom it is a matter of acute thrombosis, in a horizontal position, for, as stated by BAUER, to have a uniform technique also for patients who cannot be moved. Preferably the contrast is injected percutaneously in some vein or other on the dorsal and lateral side of the foot. If this is impossible the subcutaneous vein below the lateral malleolus is exposed.

Fig. 4. Retention of the contrast distally to the calf, the patient supine. 3 min. between the exposures.

In chronic thrombosis the technique is varied. Pictures are then taken with the patient supine, with his leg horizontal or flexed, and also in a standing position. The period of injection is about 30 sec. Contrast: Perabrodil or Uriodone 10—20 cc. Size of the film 15 × 40 or 40 × 50 cm. in 2 sections. Pictures are taken after 2 min. or more if necessary, to point out retention of the contrast. Important is also a control of the blood-stream during fluoroscopy. Pictures ought to be taken laterally, specially to decide whether the vein is a deep or a superficial one, an observation particularly important in the diagnosis of thrombosis. In the lateral pictures the sedimentation phenomena described by LINDBLOM and KJELLBERG may easily be stated.

To be discussed in the present paper and of special interest are the passage of the blood-stream in the veins of the calf, and the following question: How are the conditions of the normal blood-stream, when the leg is in horizontal position, the pressure of its own weight against the support. It is probable namely that purely mechanical conditions (pressure against the veins), specially during rest in bed, may play an important rôle in the development of thrombosis.

In 29 normal cases venographic examinations have been made with a view to these conditions. Thus mostly roentgen-physiological examinations will be reported in the following.

With the patient in the supine position, his extremities horizontal, *without* the calf against the support, the injected contrast passes almost immediately through the deep veins (Fig. 2). If the injection is made comparatively slowly and with 10 or 20 cc. of contrast, hardly any superficial veins are visible. If the contrast is injected more rapdily and in larger quantities there will be filling also of the superficial veins, and as a rule these are evacuated somewhat more slowly than the deep ones. Generally all the veins are emptied of contrast after 2—3 min. Our ob-

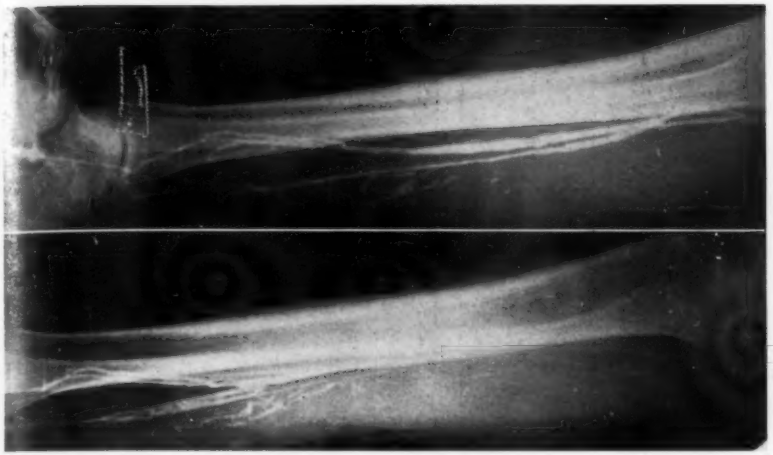

Fig. 5. A) Lateral view shows normal deep venous trunks (the leg suspended). B) Dislocation and pressure against the veins the extremity resting upon the support.

servations in this point thus show accordance with the works of BAUER and HELLSTEN, in which the main routes of the blood-stream in surae is claimed to be the deep venous trunks.

In the usual supine position the leg is mainly supported on the calf and the heal. Of course here are considerable variations, dependent on thickness of the calf and the degree of extension. When the musculature of the calf is powerfully developed the leg is resting like on a pad, corresponding to gastrocnemius, and the pressure may then, as it will be seen, have influence upon the blood-stream in the extremities. In thin patients the weight is put more on the gluteal musculature and on the pelvis, so that the pressure against the deep venous trunks of the leg becomes minimal. In bed, where the heal is pressed more or less down into the mattress, the pressure may in some cases be heavier on the calf than when the patient is lying on an even and hard table. Heaviest of all the pressure will naturally be, if the calf is placed upon a small pillow and the entire weight is resting on this.

These conditions are seen reflected in most venographies (Fig. 3). In this picture, taken of a patient with a highly developed calf musculature, it is seen how the contrast is stopped in the deep veins, and then fairly forced out into the superficial veins. There will thus be a defective filling of the deep veins, in distribution wholly corresponding to the muscular pad of the calf. If the leg remains for some time in this position a retention of contrast in the deep venous trunks, extended to about

Fig. 6. Fig. 7 A. Fig. 7 B.

Fig. 6. Venogram, the patient crossing his legs, reveals pressure on the deep venous trunks.

Fig. 7. Venogram before (A) and immediately after motion of the foot (B). The contrast has completely disappeared.

10—15 cm. distal to the muscular pad of the calf, is shown. The contrast may be observed here for 3—4 min. or more (Fig. 4). Once some of the contrast has passed through the deep veins and the extremity is kept perfectly quiet, the retention may be most pronounced corresponding to triceps surae. A *lateral view* (Fig. 5) shows how the deep venous trunks are pressed forward so much as to be partly hidden behind the tibia and fibula and then necessarily will be pressed against membrana interossea, which is suspended between these bones. Evidently these conditions must be important both for the interpretation of roentgen pictures of thromboses, and to the very diagnostical technique. Undoubtedly, as claimed by BAUER, it is important to concentrate on a technique rendering filling essentially of the deep veins. Therefore, when it is a question of making the diagnosis of acute thrombosis, the contrast is injected comparatively slowly, always with a tourniquet applied, and the lower extremities lying freely suspended above the table or the bed.

Regarding the diagnostics, we are at present able to establish the

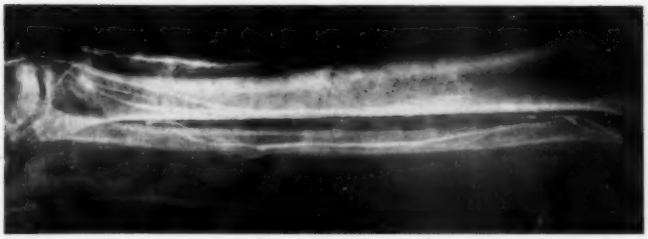

Fig. 8. Venogram in plaster cast reveals normal passage through the deep venous trunks.

fact that a roentgenogram taken with the extremity resting heavily upon the support, may completely resemble the picture of thrombosis. Another established point is the following: In the place where spontaneous thrombosis frequently arises, the venous system of the lower extremities is the most vulnerable, and particularly in passive supine position it is easily exposed to a pressure capable of compressing the veins and completely or partly interfering with the passage of blood. It must also be considered if other conditions interfere with the venous circulation in the legs.

A rather ordinary position of the patient in bed is *crossing* of the legs. Venograms from a patient in this position show that the veins in both legs are subjected to a pressure. (Fig. 6.) A retention of the contrast distally to the pressure can also be stated.

If the veins are straight and smooth it is seen that the contrast is more easily emptied than when looped and varicous. This is a well-known fact and has earlier been described inter al. by BAKER, SEDWITZ, LESSER and RAIDER.

In fluroscopy it is seen how the contrast in normal cases rapidly enters into the deep veins, and that the stream of blood is highly dependent on *motion* of the extremity. Some bending and stretching of the foot, *i. e.* contraction of the sural musculature suffice for immediate emptying the contrast. This is also easily shown by taking pictures before and after movements of the foot (Fig. 7). Similar observations have earlier been made inter al. by ÅGE NILSEN. As it will be known, he attributes decisive importance to the mechanical factor in the question of thrombus formation, and like many others, increasingly considers this point where prophylaxis is concerned.

A clinical experience shows that patients with plaster cast on their leg relatively rarely develop thrombosis. Venography reveals the passage in these cases to be undisturbed, and the deep venous trunks not to be compressed. (Fig. 8.) The *plaster cast* evidently forms a protecting cap-

Fig. 9. Fig. 10.

Fig. 9. Deep thrombosis. The leg in plaster cast. (Fracture.) Collaterals developed.

Fig. 10. Retention of contrast in the deep venous trunks during operation. Venography on the operating table.

sule around the leg and prevents compression. This rule is not true for all cases, and personally we have seen a patient in plaster cast for crus fracture, and with thrombosis in his leg. It was then possible clearly to distinguish the veins, and likewise to decide that none of the contrast passed through the deep veins only trough the saphenous trunk (Fig. 9). There is nothing special to this finding, but it is quite interesting to know that venography is able to disclose a thrombosis inside a plaster cast, when the usual clinical examination is impossible. Finally, a number of patients have been venographically examined on the *operating* table. It is an early theory that the thrombosis dates back to the operating table. In this hospital the patients during operation are attached to the operating table with a fairly tight bandage across the knees, such that the leg is somewhat pressed against the table. This is, as known, a rubber mattress that is comparatively soft and the position is not always horizontal. We have been able to point out a slight pressure against the legs and retention of contrast (Fig. 10) in some cases, but no complete obstruction.

In general and in spinal anesthesia the veins of the legs are conspicuously filled and distended, and puncture as a rule easily made. The impression is obtained that the blood circulation in these forms of anesthesia proceeds comparatively rapidly, and considerably more rapid than in a patient who has remained in bed inactive for several days.

SUMMARY

After mentioning the venography as a means to diagnose thrombosis, the fact that spontaneous thrombosis often arises in the deep venous trunks is emphasized. Contributing to the understanding of *why* this is so, venographical examinations made are re-

fer ed. It is pointed out that the deep venous trunks are liable to compression and dislocation if the entire weight of the leg is resting upon the calf, and that the contrast is retained. Further the dominant influence of motion of the extremity upon the blood-stream is explained. Inside a plaster cast there is hardly any compression of the deep venous trunks. Venographs taken on the operating table have revealed a slight degree of contrast retention, but no pronounced compression of the veins.

ZUSAMMENFASSUNG

Nach Erwähnung der Venographie als ein Mittel zur Diagnose der Thrombose wird betont, dass in den tiefen Venenstämmen oft spontane Thrombosen auftreten. Als Beitrag zum Verständnis der Ursache dieser Erscheinung wird über vorgenommene venographische Untersuchungen berichtet. Es wird darauf aufmerksam gemacht, dass die tiefen Venenstämme zu Kompression und Dislokation neigen, wenn das ganze Gewicht des Beines auf der Wade ruht, und dass die Kontrastmasse zurückgehalten wird. Ferner wird die überragende Bedeutung der Bewegung der Extremität auf dem Blutstrom erklärt. In einem Gipsverband findet fast gar keine Kompression der tiefen Venenstämme statt. Auf dem Operationstische aufgenommene Venographien haben einen leichten Grad von Kontrastretention ergeben, aber keine ausgesprochene Kompression der Venen.

RÉSUMÉ

Après avoir mentionné le rôle de la veinographie pour diagnostiquer les thromboses l'auteur souligne qu'une thrombose spontanée survient souvent dans les troncs veineux profonds. Pour contribuer à la compréhension du »pourquoi», il apporte les examens veinographiques qui furent pratiqués. Il fait remarquer que les troncs veineux profonds sont exposés à être comprimés et déplacés lorsque tout le poids de la jambe appuie sur le mollet, et qu'en pareil cas la substance de contraste est sujette à de la rétention. Puis il explique l'influence prépondérante des mouvements sur le courant Sanguin. A l'intérieur d'un appareil plâtré il n'y a guère de compression des troncs veineux profonds. Des veinographies prises sur la table d'opération ont montré un léger degré de rétention de la substance opaque, mais pas de compression prononcée des veines.

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BOOK REVIEW.

BULL ENGELSTAD, ROLF: *Stråleterapi. Lærebok i Röntgen- og Radiumbehandling. (Radiotherapy. Text book of Roentgen and Radium treatment).* JOHAN GRUNDT TANUM, *Oslo.* 1946 (388 *pages, Norwegian*).

BULL ENGELSTAD has written a textbook of radiotherapy which, to a great extent, is based on the experiences relating to indications and methods gained at the Norwegian Radium Hospital (Det Norske Radiumhopital). Radiotherapy is so new a science that, in many respects, its methods are still in the experimental stage. Different countries and different clinics have solved the same therapeutical problems in various ways and, in many respects, it is still very difficult to say which solutions are best. As the author points out in his preface, it seems almost impossible, within the scope of a textbook, to do justice to the different schools and methods. It is for this reason that, on the whole, the author deliberately contents himself with expounding the routine methods of the Oslo Clinic. It is only in especially important instances that he has quoted foreign authors.

The Oslo Clinic is one of the youngest centres for radiotherapeutics in the world, and it has had many prototypes in matters concerning organisation, equipment, indications and methods of treatment. On the whole one can say that the Norwegian radiotherapy which the textbook expounds is a synthesis between impulses from the Paris School (Institut du Radium), the Stockholm School (Radiumhemmet) and personal contributions by Norwegian radiologists.

Those parts in the author's work where some doubt is felt by a Swedish radiotherapeutist are, quite naturally, to be found where the French influence is preponderant. Some instances can be given: Coutard's method in fractional roentgen treatment is highly recommended in many places in the book and, amongst other things, is said to have the advantage of causing relatively little damage to healthy tissues. There are many investigations during recent years which cast doubt on the Coutard thesis. In Sweden we are of the opinion that ordinary fractional roentgen treatment gives just as good results as the protracted form which, on account of the lengthy irradiation times, is both unpractical and expensive. Further we consider that the surface application of radium (»moulage treatment») is an uncomfortable method in malignant tumours which can most often be advantageously substituted by other forms of radium treatment or roentgen treatment. As a third instance it can be said that in Sweden the tumour form which is called lymphoepithelioma (REGAUD and others), has been abolished, at least as far as tonsils and pharynx are concerned. We now assign these growths partly to low differentiated carcinoma and partly to reticulum cell sarcoma.

We must remember, however, that the differences are not fundamental and that in other countries, in Denmark and Finland for instance, one is often of an opinion which coincides more with the Norwegian.

Most of the textbooks of radiotherapy which have hitherto been published are partly rather incomplete and one-sided and partly out of date. BULL ENGELSTAD thus has not had access to any real prototypes. This fact emphasizes the book's character of beeing both an original and an important work. One must admire the author's wide reading and energy and also his extraordinary gift of being able to weigh up successfully the proportions between the many and widespread branches of his subject (radiophysics, radiobiology, radiopathology, clinics, technique of treatment). The author shows an exceptionally sound and good judgement and so has managed generally to avoid being too dogmatic and categoric in his opinions which is so usual with textbook authors. It is also very pleasing for a Swede to note BULL ENGELSTAD's anxiety to stress the importance of »the principle of the least possible dose». In all probability Professor GÖSTA FORSSELL is the one who has fought for the greatest length of time and with so much energy just for this principle which is so obvious to us now.

The book is easily read and clear. The chapters on physics and biology are therefore particularly easily accessible without, in any way, losing in detail and fact.

The book contains quite a large number of well chosen and good illustrations.

The author himself says that his chief reason for writing the book was to help students and doctors who are not radiologists. One might add that it should prove very useful as a reference book even for radiologists, especially, perhaps, for those who devote much of their time to roentgen diagnosis but who are faced now and again with therapeutic tasks and problems. It is nevertheless to be regretted that it wasn't possible to include more quotations as well as bibliographic references and that the text was not further sub-divided with a great number of subheadings. If there had been, the book would have been even more valuable as a reference book for radiologists and it had probably gained in accessibility and lucidity.

The book is warmly recommended.

H. Ahlbom.